Monographs on Surgery • 1950

MONOGRAPHS ON SURGERY • 1950

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THOMAS NELSON & SONS
Toronto NEW YORK Edinburgh

PRINTED IN THE UNITED STATES OF AMERICA

Introduction

THE PUBLICATION of this volume marks a distinct change in the policy of the editors and publishers of *Nelson's Loose-Leaf Surgery* and consequently deserves an explanation.

The present volume represents the initial effort in this direction. Instead of the loose-leaf form, a bound volume is to be offered annually. This volume will contain monographs on significant surgical subjects of varied interest, covering the field of general surgery as well as the specialties of gynecology, orthopedics, and urology. Subjects to be covered will be those in which recent and signal advances have been made, but material which is still in an experimental or questionable stage will be deferred until reasonably conclusive work has been done.

The initial volume presents a group of papers on topics regarding which there is a fair degree of unanimity of opinion. No attempt has been made to correlate the various subjects discussed. In future volumes, however, the editors hope to present several monographs on related subjects or on the same subject considered from different points of view In this manner, the previous set of volumes will eventually be completely replaced

Particular attention has been directed toward the adequacy and significance of the material published about the surgical specialties, and an associate editor has been appointed for each The men selected are outstanding in the fields for which they are responsible, and include Dr Charles B. Huggins as Associate Editor for Urology, Dr. J. V Meigs as Associate Editor for Gynecology, and Dr. A. R. Shands, Jr., as Associate Editor for Orthopedics.

It is to be hoped that this new purpose will be adequately fulfilled and that Nelson's *Monographs on Surgery* will prove valuable in the better understanding of currently significant surgical topics.

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Chemotherapy in Surgery

Chemotherapy in Surgery

W. A. ALTEMEIER, M.D.

STRICTLY SPEAKING, chemotherapy is the treatment of disease by chemical agents, but the conception of the term at the present time is usually limited to the administration of chemical agents which are capable of selectively inhibiting or destroying the growth of infecting micro-organisms *in vivo* without marked or serious toxic effects on the host. The infecting micro-organisms may be pathogenic bacteria, viruses, spirochetes, Rickettsia, yeasts, fungi, or parasites. In the decade 1920 to 1930 the treatment of infections by chemical agents was in general disrepute, but during the past 15 years successful chemotherapy not only has become a reality but even a beneficial influence on practically all branches of surgery.

HISTORY

Throughout its history, surgery has advanced largely through important contributions made by the various basic sciences. Philosophy, anatomy, pathology, physiology, bacteriology, and biochemistry have each in turn contributed to its development. With the onset of the bacteriologic era and the establishment of the bacterial concept of infection, physicians, bacteriologists, and chemists began their search for chemical agents which would control infection by destroying the bacteria in the tissues. They found many which killed bacteria *in vitro* even in high dilutions, but the very qualities which made them bactericidal caused them also to be toxic to human tissues, usually producing redness, swelling, induration, delayed healing, and often an increased incidence of infection. So universally true was this, that as late as 1935 the goal of chemotherapy was still a dream in the minds of surgeons. Before that time, however, considerable preliminary experimental work which was to permit the realization of this dream had been done.

Although chemotherapeutic agents had not been developed for clinical use, the existence of such substances has been known for many years. The effect of quinine on malaria has been recognized for a long time, and as far back as 1877, Pasteur and Joubert had observed bacterial antagonism between certain airborne bacteria and the anthrax bacillus, the growth of the latter being inhibited b[illegible] former. They had also suggested that it might be possible to use t[illegible] of certain infections. Later Emmerich and Loew [illegible]yocyanase from cultures of [illegible] [illegible] [illegible]

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properties, pyocyanase has never become [illegible]

Paul Ehrlich was an important pioneer in the field of chemotherapy. After many years of experimentation, he found trypan red which destroyed trypanosomes and salvarsan, which had a selective effect on the spirochete of syphilis. In 1908, Gelmo synthesized para-amino-benzene sulfonamide and in 1909, Herlein, in co-operation with others at the I. G. Farbenindustrie, synthesized the first azo dyes which contained the sulfonamide group. When these dyes were tested, those having the sulfonamide group were found to be superior in color fastness to those which did not. The possibility that these compounds might react with bacterial protoplasm was suggested and experiments were undertaken to determine whether or not they possessed antibacterial activity. In 1913, Eisenberg demonstrated that they did. Heidelberger and Jacobs concluded that para-amino-benzene sulfonamide was bactericidal, and they reasoned that it might be liberated in the tissues in the metabolism of the sulfonamide, chrysoidin. However, the full significance of these early observations was not realized.

While he was serving as a British medical officer in World War I, Fleming (1915-1918) became interested in the antibacterial power of leukocytes contained in pus from wounds. His search for a differential antibacterial agent was unsuccessful at that time, and he also learned that the destruction of leukocytes by wound antiseptics often robbed the body of one of its natural protective mechanisms. Later, in 1922, he described lysozyme, a rather potent antibacterial ferment which was of academic interest only.

In 1924, Gratia and Dath described for the first time another antibacterial substance known as actinomycetin, which was produced by certain strains of the Actinomyces.

In 1928, Fleming, while working with staphylococcal variants, made the important observation that the bacteria on an agar plate immediately about a contaminating colony of a mold had undergone spontaneous lysis. Many bacteriologists had undoubtedly thrown away similar contaminated culture plates without recognizing the significance of the bacterial antagonism which was occurring. However, to Fleming the appearance of the culture plate was such that he thought that it should not be neglected, and he began to investigate its significance. He determined that the mold belonged to the genus Penicillium, and he preserved it by subculture. In broth filtrates of the mold, he demonstrated the presence of an active principle which he named penicillin. By extraction, Fleming produced penicillin in an impure form with remarkable selective antibacterial properties. It inhibited the growth of a variety of gram-positive bacteria, but was essentially ineffective against gram-negative bacteria, including *B. coli* and *H. influenzae*. Fleming utilized the active principle of penicillin in broth filtrates in his laboratory to eliminate gram-positive bacteria from the gram-negative in differential culture work, and he made certain observations which showed that this agent was relatively nontoxic for animals and their cells, including the leukocytes. After suggesting the potential value of this agent in clinical medicine, Fleming was the first to use it for irrigation of infected conjunctivae and large wound surfaces in human beings. No evidence of irritation or toxicity followed topical use of the broth filtrates in this manner.

Clutterbuck, Lowell, and Raistrick, in 1932, were successful in growing the mold on synthetic media, but they could not extract penicillin from the liquid

in a stable and purified form. In 1935, Reid in America reported antibacterial activity of broth cultures containing penicillin. Fleming originally thought that his mold was *Penicillium rubrum*, but later it was identified as *Pencillium notatum* by Thom who performed his studies at the request of Clutterbuck and his colleagues at the University of London. The development of penicillin then became stationary for the following seven years.

Meanwhile, work on the sulfonamide compounds continued at the I. G. Farbenindustrie, and in 1932 a German patent was obtained by Klare and Mietzsch which covered prontosil and other azo dyes containing the sulfonamide group. At this time, the Germans under Professor Horlein assembled a group of investigators consisting of Domagk, Mietzsch, and Klare in the Elberfeld Laboratory of the I. G. Farbenindustrie in an attempt to find some chemical agent which had a selective action on streptococci in anticipation of the coming of World War II. As a result of their investigations, they observed in 1932 that an azo dye, the hydrochloride of 4-sulphamido-2:4 diamino-azobenzol which was known as prontosil, had a selective action for hemolytic streptococci in experimental infections of mice. Domagk's observations were not published until 1935, and immediately thereafter they led to the extensive use of this drug in human infections. For this he was offered, but refused, the Nobel Prize in Medicine.

Trefonels, Nitti, and Bovet of the Pasteur Institute also demonstrated in 1935 that in animals the azo dyes were split at the azo linkage, and that prontosil yielded para-amino-benzene sulfonamide, the compound originally synthesized by Gelmo in 1908. They postulated that para-amino-benzene sulfonamide was the active therapeutic portion of prontosil, and Fourman proved this experimentally in 1936. English investigators then became interested in the possibilities of the sulfonamide-containing azo dyes, and the reports of Buttle in 1935 and of Colebrook and Kenny in 1936 stimulated widespread interest in the compounds in Europe and America. Well organized clinical studies quickly revealed its practical value. The Council on Pharmacy and Chemistry of the American Medical Association reported on para-amino-benzene sulfonamide in 1937 and suggested that it be named sulfanilamide.

The discovery of the selective effect of prontosil reopened the whole field of chemotherapy and stimulated intense activity among chemists and pharmacologists in an effort to produce new and related compounds having greater antibacterial activity, improved pharmacologic properties, and lower toxicity. Of the many sulfonamide compounds that were synthesized, only a few were suitable for clinical trial or actual use, and most were eventually discarded.

At the Rockefeller Institute for Medical Research, Dubos in 1939 found that the *Bacillus brevis*, an aerobic motile spore-forming organism isolated from soil, produced a highly bactericidal substance for gram-positive organisms which he named tyrothricin Subsequently, he showed tyrothricin to be a mixture of tyrocidine and gramicidin, so named because of its high activity against gram-positive bacteria, and in memory of H.C J. Gram. However, the material was found to be extremely toxic for experimental animals, killing them in a matter of seconds after intravenous administration. This fact limited its usefulness as a chemotherapeutic agent to local applications in small quantities.

Meanwhile, Florey and his associates at the William Dunn School of Pathology

at Oxford, England, had been interested in antibiotic substances since 1929, when they had begun studies on lysozyme discovered by Fleming in 1922. Their investigations of this substance were abandoned when it was learned that it behaved as an enzyme and that it was not very effective against pathogenic bacteria Florey and Chain decided to make an intensive survey of naturally produced antibacterial substances in 1938. Among the first antibiotic substances investigated briefly by them were the products of *B. pyocyaneus*. After many unsuccessful attempts to find an effective antibacterial agent, they decided in 1939 to examine penicillin, despite the earlier reports that it was very unstable. Dubos' work at this time had also stimulated their interest in the study of antibacterial agents of biologic origin. The earlier observations of Fleming, Clutterbuck, and others that the activity of penicillin could be maintained in the original media for several weeks indicated to Florey and Chain that the agent would not be too unstable to warrant investigation. In August 1940, the results of this co-operative study on penicillin by Florey, Chain, Abraham, Gardner, Heatley, Jennings, Orr-Newing, Saunders, Fletcher, and Florey, along with a number of surgeons and physicians, were published The report included details of their methods for the purification of penicillin, their investigations of its antibacterial properties *in vitro*, and their observation of its therapeutic effect in animals. These investigations were remarkable also because they were accomplished under the stringencies imposed by the darkest moments of World War II, in which the British were then engaged One of their chief difficulties was the large amount of culture material required to produce enough penicillin with which to treat one patient

In 1941, the same group of investigators described the preparation of a fairly well purified product of penicillin and included the first reports on the possible clinical value of the material. After several months' work, they had obtained enough material for injection in a human being This first injection was followed by a reaction of the patient, including chills and fever, which they found to be due to impurities and not to penicillin. In addition, they were able to reclaim the penicillin in a fairly purified state from the urine of one of the early patients, indicating that passage through the human body resulted in purification.

The intensive bombing of England and the stringencies imposed by limited personnel, space, and materials made it impossible for the English to produce penicillin in great quantities Accordingly, in the summer of 1941 under the sponsorship of the Rockefeller Foundation, Florey and Heatley visited the United States to stimulate interest in penicillin and to secure help in the problems involved in its large scale production They consulted the individuals most interested in chemotherapy and micrology, including Charles Thom, the principal micrologist in the United States Department of Agriculture at Washington, D C, the Committee on Medical Research of the Office of Scientific Research and Development, and Coghill of the Northern Regional Research Laboratory of the Department of Agriculture Arrangements were made for consultation with various commercial houses interested in the development of penicillin, who then undertook in earnest its large scale production After his return to England, Florey conducted clinical studies on the battlefronts in North Africa and Sicily. Fleming and Florey were later knighted by King George VI of England for their

outstanding contributions to the problem of bacterial infection in the armed forces and civilian population.

Although the credit for the development of penicillin goes primarily to the British investigators, some interest in penicillin had been present in the United States during the same period. Reid had studied broth filtrates containing penicillin and attempted to isolate the active substance by distillation at low temperatures in 1935. In 1940, Bornstein reported on the antibacterial action of penicillin in broth filtrates and in May 1941, a fairly active preparation of penicillin was reported by a group at Columbia University including Dawson, Meyer, Hobby, and Chaffee.

The National Research Council's Committee on Chemotherapeutic and Other Agents, composed of Keefer, Blake, Lockwood, Marshall, and Wood, began in 1942 to organize and supervise studies throughout the United States on penicillin and other agents which might be valuable in the treatment of susceptible bacterial infections, particularly those anticipated in war. A group of accredited American investigators working in a number of medical centers was appointed by this committee; it included Altemeier, Blumfield, Dawson, Elmond, Hershfield, Horsfall, Hutter, Lyons, Mahoney, McClure, McKhann, Meleney, Nelson, Parks, Richards, Robb, Smith, Spink, and Tillett.

In 1942, Waksman and Woodruff recovered another antibacterial agent, streptothricin, from cultures of *Streptomyces lavendulae*. This substance was shown to have a selective bacteriostatic action against a variety of gram-negative and gram-positive bacteria. Unfortunately, it produced a delayed toxicity, causing the death of mice several days after injection, a phenomenon even more marked in larger animals such as the monkey. Waksman and his associates then turned to other related organisms, and in 1944, Waksman, Bugie, and Schatz succeeded in growing *Streptomyces griseus*, an organism previously isolated in 1916, from heavily manured field soil, on special media and found that it produced a highly effective antibacterial substance which they called streptomycin. This agent was of particular interest because it exhibited *in vitro* activity against a wide range of bacteria, including gram-negative as well as gram-positive organisms. It also inhibited the growth of the *Microbacterium tuberculosis* in a dilution of 1:30,000. Like penicillin, the parenteral administration of early preparations of streptomycin caused reactions which were disturbing. These included flushing of the face, throbbing headaches, nausea, vomiting, joint pains, skin rash, and drug fever which occurred after two or three days of treatment. More highly purified preparations from which the impurities were eliminated did not cause these acute reactions.

Meleney, Johnson, and Anker reported in 1945 the discovery of another antibiotic agent produced by the Tracey strain of *Bacillus subtilis* which was recovered in May 1943 from a culture of debrided tissue removed from a compound fracture in a patient whose name was Tracey. Their studies indicated that bacitracin was neutral, water-soluble, nontoxic, and relatively heat-stable. Bacitracin was shown to have a wide antibacterial spectrum similar to that of penicillin, being effective against many strains of the large group of gram-positive bacteria.

In February 1946, *Bacillus aerosporus*, an organism isolated from the soil of an

English market garden during a systematic program for the antibiotic screening of soil bacteria, was found by Ainsworth, Brown, and Brownlee to produce a new antibiotic substance highly active against gram-negative bacteria. The organism was identified by Proom as *Bacillus aerosporus*, and the antibacterial substance was originally designated as aerosporin. Stansly and others reported the extraction of polymixon from cultures of *Bacillus polymixa*. However, it has been established that the *Bacillus aerosporus*, originally found in Chicago tap water by Greer, and the *Bacillus polymixa* are the same. Several antibiotics derived from *Bacillus polymixa* have been differentiated. Those originally described by the British workers were formerly designated as aerosporin, bacillosporin A, bacillosporin B, etc. Recently, however, it has been agreed among the principal investigators that the various antibiotic agents derived from *Bacillus polymixa* henceforth will be designated as polymixon A, polymixon B, etc The most promising one, aerosporin or polymixon B, has a highly selective antibacterial activity for gram-negative organisms It has not been adopted for general clinical use because of some toxic manifestations which have occurred and because of the current availability of streptomycin which is superior in its action in many respects.

Aureomycin is an antibiotic recently derived from a strain of *Streptomyces aureofasciens*. It has been found to be active against a large number of bacteria *in vitro* and has shown considerable promise in the treatment of a variety of clinical and experimental infections, particularly those resistant to penicillin, sulfonamides, and streptomycin, and various rickettsial and virus infections. Two of its advantages include ready absorption after oral administration and considerable antibacterial action *in vitro* against a wide range of gram-positive and gram-negative bacteria From all present indications, this antibiotic agent is a valuable addition to the field of chemotherapy.

Chloromycetin is another promising new antibiotic agent which has been derived from a soil actinomycete, *Streptomyces venezuelae*, originally isolated from a sample of soil collected in a mulched field near Caracas, Venezuela. When the organism was grown in liquid media, it produced a substance with marked antibacterial activity against a large number and variety of micro-organisms. Biologic studies showed its spectrum to include effective inhibition of various gram-negative bacilli including *H. pertussis*, *B coli*, *Brucellus suis*, *Brucellus melatensis*, *E typhosa*, *Proteus vulgaris*, and Salmonella. It showed less activity against the tubercle bacillus and was least active against the gram-positive cocci In some gram-negative bacillary infections, it has been more effective than streptomycin It has no value in protozoan or fungus infections. Like aureomycin, it may be given effectively by mouth Clinical studies have also indicated its value in the control of certain virus and rickettsial infections. It likewise appears to be a valuable addition to the field of chemotherapy.

The search for new chemotherapeutic agents continues at an accelerated pace and in a rather systematic manner At the present time, the tendency is for many different groups of investigators to specialize on certain groups of bacteria or plants as possible sources of new antibacterial compounds. Up to February, 1949, over 100 antibiotic agents have been described, and uncounted others are under investigation The exploitation of the therapeutic possibilities in the field of chemotherapy is obviously still in a preliminary degree of development.

GENERAL CONSIDERATIONS

Chemotherapeutic agents may be either of biologic or non-biologic origin. Compounds which are derived from living cells and are destructive for other living cells are designated antibiotic agents or antibiotics. Strictly speaking, the term antibiotic means "against or destructive of life," but recent developments have restricted the term to antibacterial agents derived from living molds, bacteria, yeast, and other animal cells.

The chemotherapeutic agents of non-biologic origin include various organic and inorganic chemical agents, the great majority of which are produced synthetically. It is significant to note, however, that man has been much less successful in making antibacterial agents than nature. From all the synthetic compounds of the heavy metals, oxidizing agents, coal tar derivatives, phenols, azo dyes, oils, etc., he has developed only a few which can be classified as chemotherapeutic agents, and none of these is as effective as the better antibiotic compounds. The sulfonamides are the most important agents of non-biologic origin thus far discovered.

Chemotherapeutic agents of biologic origin include those produced by the higher plants, micro-organisms, and higher animals. They may be bacteriostatic, bactericidal, or both. Their action is selective but their mode of action on micro-organisms and their toxic manifestations vary greatly. Among those of relatively minor importance which occur naturally in the plant kingdom may be mentioned quinine, emetine, and chlorophyl. Of these produced naturally by a large number of molds, bacteria, and yeasts may be listed penicillin, actinomycetin, actinomycin, aureomycin, bacitracin, chloromycetin, citrinin, clavacin, fumigatin, gramicidin, penicillic acid, polymixon, pyocyanase, pyocyanin, streptomycin, streptothricin, and tyrocidin.

Some investigators maintain that bacteriophage is an enzyme-like substance closely akin to the chemotherapeutic agents. Of all these, only penicillin, streptomycin, aureomycin, and chloromycetin are in general clinical use at present, while bacitracin, tyrothricin, and the polymixons are in limited clinical use. Included among those which occur naturally in the animal kingdom are lysozyme, which is present in tears, saliva, and a variety of animal tissues, lactenin, and the active bactericidal substance produced by the maggot *Lucilia sericata.*

The ideal chemotherapeutic agent is one which possesses a high bacteriostatic or bactericidal effect for infecting micro-organisms such as pathogenic bacteria, spirochetes, viruses, yeasts, fungi, etc., and a low toxicity for the host. In contrast to most antiseptics, which act as general protoplasmic poisons immediately or irreversibly affecting morphologic structure or metabolic systems common to living matter, chemotherapeutic compounds possess a selective or specific destructive effect on some metabolic phase of the etiologic agents of infection. The nature and mechanism of these metabolic disturbances vary from one compound to another Some of the compounds possess bactericidal properties, being capable of selectivity killing bacteria *in vitro* Others have bacteriostatic properties which appear to inhibit the proliferative activities of micro-organisms or to interfere with other important metabolic functions in such a manner that their final destruction or removal from body fluids and tissues is accomplished by phagocytosis or other immunologic responses. It is not necessary for a chemotherapeutic agent to

kill bacteria *in vivo* to be effective, and the therapeutic properties of most of the chemotherapeutic agents seems to depend largely upon their bacteriostatic activity.

In some instances, the difference between bacteriostatic and bactericidal activity, however, is quantitative rather than qualitative, depending upon certain factors which affect the rate at which irreversible changes occur within the inhibited cells Dubos stated that the acidic or basic properties of chemotherapeutic agents for bacteria may influence their specificity or selective activity, as may also the nature and properties of the membranes of bacteria, their permeability, the relative viability of their specific biochemical systems, and the activity of autolytic enzymes. Many gram-negative bacillary forms behave in relation to chemotherapeutic agents more like animal tissue cells than micro-organism cells. In regard to the nature of infectious agents, there is considerable evidence to show that bacteria, spirochetes, and protozoa are far more susceptible to chemotherapeutic agents than are Rickettsia, viruses, and fungi. The micrococci as a group, both gram-negative and gram-positive, are more susceptible to antibacterial compounds than the bacilli

PHARMACOLOGIC AND THERAPEUTIC CONSIDERATIONS OF THE AVAILABLE CHEMOTHERAPEUTIC AGENTS

Although an almost countless number of chemical agents of biologic and nonbiologic origin have been shown to exhibit antimicrobial activity *in vitro*, only a few retain this property *in vivo* and are sufficiently low in toxicity to warrant their use as chemotherapeutic agents for the control of infectious lesions. The pharmacologic and therapeutic aspects of the various chemotherapeutic agents will be discussed in detail, those whose clinical value has been well established, and those which are under intensive investigation at the present time. The antibacterial compounds that will be considered are the sulfonamides, penicillin, streptomycin, aureomycin, chloromycetin, bacitracin, and polymixon. Another group of antibiotic agents which apparently does not have great clinical potentialities will be described briefly

Sulfonamides

Of the many thousands of compounds of nonbiologic origin synthesized after the demonstration of the antistreptococcal activity of prontosil in 1932-1935 in the search for more effective and safer antibacterial agents only a few were satisfactory for clinical trial and actual use. Only sulfanilamide and several of its chemical derivatives or closely related compounds have been used widely in clinical practice

The sulfonamides as a group are essentially bacteriostatic compounds of relatively low solubility, marked selective antibacterial action, and variable toxicity

The mode of action of the sulfonamides is not that of a bactericide or of an antiseptic, but that of a bacteriostatic agent which exerts its effect on bacterial metabolism and inhibits bacterial growth The observation of Colebrook that these agents were bacteriostatic rather than bactericidal, except for very small inocula of organisms, has been confirmed repeatedly by many other workers in

this field. Lockwood and his associates concluded that sulfanilamide altered the total metabolism of the micro-organism and produced a striking depression of its invasive properties. In support of this theory, it has been observed that the sulfonamides are most effective at a time when the micro-organisms are growing most rapidly. The important effect of the sulfonamides is in the tissues, and they must be absorbed in order to influence invading and proliferating agents of disease.

Absorption of the important sulfonamides occurs readily after oral, intravenous, subcutaneous, or intramuscular administration. Once they are absorbed, the sulfonamides are all very diffusible, appearing rapidly in the body fluids, wound exudates, cerebrospinal fluid, and urine. Within the body a certain proportion of each of the sulfonamides is inactivated by the process of acetylation which takes place in the liver. Relatively insoluble acetyl derivatives are thus formed which may be precipitated in and cause damage to the kidneys. Each of the sulfonamides, when given systemically, seems to have deleterious effects as well as therapeutic value, and it is essential to have a complete and detailed knowledge of their action before their extensive use is undertaken. The original sulfonamide, prontosil, is rarely used in this country at this time.

Sulfanilamide, known chemically as para-amino-benzene-sulfonamide, is the parent sulfonamide. It is the amide of sulfanilic acid.

It is a white crystalline substance with a slightly bitter taste. It is soluble in hot water, hot alcohol, and acetone; slightly soluble in cold water (0.8 to 1.0 per cent), and cold alcohol, and insoluble in benzene, chloroform, and ether. Sulfanilamide is an amphoteric material which is capable of forming salts with both strong acids and bases. Its melting point is 165° to 167° C. Sulfanilamide has practically been discarded in favor of its later derivatives because of its relatively limited activity and its relatively high toxicity. The tendency to produce severe cyanosis, dyspnea, hemolytic anemia, central nervous system symptoms, and occasionally liver and kidney damage has inhibited its use. Because of its relatively greater solubility, sulfanilamide still finds limited use among some surgeons for topical application. Sulfanilamide, as well as all of its important compounds, has been found to have no effect on immune body formation.

Sulfapyridine was the first derivative to receive wide clinical use. It is known chemically as 2(p-amino-benzene-sulfonamide) pyridine.

It is a tasteless, white, crystalline compound with a melting point of 191° to 194° C and a solubility of approximately one part in 1,000, being, therefore, about one-tenth as soluble as sulfanilamide It is 0.25 per cent soluble in 95 per cent alcohol and soluble in acetone It forms water-soluble salts with strong bases and mineral acids. Sodium sulfapyridine is the basic salt and it is soluble up to 75 gm. in 100 cc. of water. Introduced originally for intravenous infusion, it has been administered subcutaneously, intramuscularly, orally, and rectally. It had the advantage of greater activity with little or no tendency to produce cyanosis, dyspnea, or hemolytic anemia It did, however, produce marked gastro-intestinal symptoms, evidence of cerebral irritation, crystalluria, and evidence of local renal irritation with hematuria and colic resulting from precipitation of the drug in the urinary tract.

Sulfathiazole was the second successful substitution product of sulfanilamide and it is known chemically as 2-para-amino-benzene-sulfonamide-thiazole, or 2-sulfanilyl-aminothiazole

It is a white crystalline powder which is practically odorless and tasteless Its melting point is 168° to 175° C, and its solubility is 96 mg. per 10 cc. of water at 37.5° C. It is soluble in glacial acetic acid, slightly soluble in alcohol, and insoluble in chloroform, ether, benzene, and ethyl acetate. Its sodium salt has an optimum solubility of 5 per cent in water and is suitable for intravenous and subcutaneous administration Although it was found to be more active therapeutically than sulfapyridine and less toxic, it produced a state of severe sensitization associated with fever, rashes, arthralgia, lymphadenopathy, and liver damage in some patients Its low solubility also produced complications in the urinary tract due to crystallization. Occasionally the rapid intravenous injection of the soluble sodium salt caused incomplete anuria as a result of precipitation of crystals of the unconjugated drug within the kidney tubules.

Sulfadiazine, the pyrimidine derivative of sulfanilamide, was the third successful derivative of sulfanilamide. It is known chemically as 2-sulfanilamido-pyrimidine

It is a white crystalline powder which is practically odorless and tasteless, and which has a melting point of 253° to 256° C., and a solubility of 0.0123 gm. in 100 cc. of water of 37° C.

It is insoluble in chloroform and ether. Sulfadiazine is unstable when boiled, autoclaved, or exposed to the sunlight for prolonged periods Clinical usage has demonstrated it to be the sulfonamide of choice in the control of surgical infections Its activity is essentially the same as that of sulfathiazole, yet it has the *advantage of lower toxicity Since it is excreted more slowly and since less of the* acetylated form is circulated, the concentration of active free drug in the blood per given dose is higher and more sustained. Although it is only slightly soluble, it causes fewer and less severe urinary tract complications than does sulfathiazole The appearance of the drug in the cerebral spinal fluid is delayed somewhat, but it soon reaches and maintains a level of about two-thirds of that found in the circulating blood In other exudates the concentration approximates that of the blood Neither sulfadiazine nor its sodium salt is absorbed in any significant amounts after its rectal administration

Sulfamerazine is a derivative of sulfadiazine which has become very popular with some surgeons, although it has by no means replaced sulfadiazine Chemically, it is known as 4-methyl-2-sulfanilamideo-pyrimidine

Recently, combinations such as those of sulfadiazine and sulfathiazole or sulfadiazine and sulfamerazine have been introduced under the premise that the two drugs will affect the kidneys in proportion to their individual concentrations, but will exert additive bacteriostatic effect Lehr *found that a saturated solution* of one sulfonamide could be fully saturated with another sulfonamide without causing crystallization or precipitation in the solution In short, each drug behaved as though it were present alone, producing no material influence on the solubility of the other. However, the antibacterial efficiency of such mixtures has been shown to correspond with the total sulfonamide content. In effect,

total therapeutic efficiency is retained but renal complications are claimed to be no greater than that anticipated with half dosage of one or the other of the sulfonamides comprising the mixture. If a combination of sulfonamides is considered desirable, that of sulfadiazine and sulfamerazine has been recommended by Long.

Sulfaguanidine, sulfasuxidine, and *sulfathalidine* are of more recent development and they have a more specialized use. They are poorly absorbed when given by mouth and are capable of reducing significantly the bacterial content of the gastro-intestinal tract. Because of this, their chief use has been in the prophylactic preoperative preparation of the gastro-intestinal tract.

Sulfanilamide and its derivatives are known to be toxic, but the degree of toxicity varies with the individual as well as the drug. Sulfanilamide gives the most diverse toxic effects and sulfadiazine the least in the whole group. A small dose, fortunately, has never caused death, even in a hypersensitive individual, but therapeutic doses can cause toxic manifestations even in the normal individual, since these drugs may interfere with the metabolism of the host as well as the metabolism of the invading bacteria.

The toxic reaction to the sulfonamides may be immediate or delayed. The immediate reactions are caused by direct effect on the patient and these symptoms disappear with the discontinuation of the drug. The remote or delayed effects are caused by the sensitization of tissues of the patient to the drug. Many of the toxic manifestations may be serious, while others may not Nausea and vomiting, headache, dizziness, delirium, acidosis, moderate anemia, marked leukocytosis, and hematuria are in themselves not necessarily serious, and will disappear quickly after the drug has been withdrawn On the other hand, drug fever, dermatitis, hepatic damage, jaundice, acute hemolytic anemia, leukopenia, granulopenia, agranulocytosis, thrombocytopenia purpura, oliguria, nitrogen retention, arthritis, conjunctivitis, scleritis, neuritis, and splenomegaly are serious or may become serious Their occurrence generally should be an indication for discontinuation of the drug and institution of proper treatment for the toxic manifestations. Hematuria and functional impairment of the kidney are more common during sulfathiazole and sulfadiazine therapy. Experimental work in the laboratory indicates that blocking of the kidney tubules and pelves or the ureters with the precipitated acetyl fractions of these drugs plays a role in the production of this toxic reaction. In some instances, permanent renal impairment in the nature of a tubular nephrosis has been observed following a toxic reaction. Other toxic reactions which have been described include stomatitis, ocular and auditory disturbances, arthralgia, gastro-enteric hemorrhage, and peripheral neuritis. Agranulocytosis is one of the most severe complications and the chief cause of death There is no evidence that pentnucleotide is of value in its treatment Hepatic disturbances have been associated more frequently with sulfanilamide than with the other sulfonamides.

Once a patient has had sulfonamide fever, rash, hepatitis, leukopenia, acute hemolytic anemia, injection of the sclerae, and conjunctiva, or purpura hemorrhagica in the course of therapy with sulfanilamide or its derivatives, he is prone to have an earlier and more severe toxic reaction if the same drug is administered again at a later date. In addition, if another member of the sulfonamide group is

prescribed, a similar toxic effect may occur. It is advisable, therefore, to determine whether or not a patient has previously had a toxic reaction during a course of therapy with one of these drugs. Generally, it is advisable to keep patients who are receiving sulfonamide therapy out of the direct rays of the sun, and away from ultraviolet or infra-red radiation in order to prevent the complication of photosensitization.

For these reasons, sulfonamide drugs must be administered with caution and controlled whenever possible by every available laboratory means White blood cell counts, hemoglobin determination, and urine examinations should always be done daily for the first three days and then every other day for the first two weeks of treatment. If hypersensitivity is suspected, it may be elicited by testing the patient with an oral dose of 0 5 gm. of the drug or less He should then be watched for 24 hours for the development of reactions such as headache, nausea, vomiting, skin eruptions, and fever.

With the exception of acute leukopenia, the presence of most of the toxic manifestations of sulfanilamide or its derivatives which occur in the first two weeks of therapy usually can be suspected by careful clinical observation. The physician should visit the patient receiving one of these drugs and should inquire as to his symptoms Headache, body aches, and malaise are often the precursors of many of the toxic reactions of sulfanilamide or its derivatives. Examinations should be made of the sclerae for congestion and jaundice, of the mucous membranes for pallor, and of the skin for rash The temperature should always be taken to determine whether or not drug fever is present. Once crystals appear in a freshly voided specimen during sulfadiazine therapy, it is necessary to adopt vigorous measures to reduce the urinary concentrations of the drug This may be accomplished by reducing or withholding the compound until the crystals disappear, by forcing fluids, and by alkalinization of the urine to permit as much as a tenfold increase in the solubility of some sulfonamides The danger of sulfadiazine precipitation in the tubules of the kidneys or ureters may be minimized by knowledge of the fact that it occurs most frequently when the urine is acid and concentrated. The forcing of fluids alone cannot be relied upon entirely to reduce the urinary concentrations of sulfonamides, and in fact this procedure may be contraindicated in patients with cardiac or renal impairment. If urinary obstruction occurs from crystals, prompt action should be undertaken to prevent the development of uremia. In addition to the increased fluid intake and administration of alkalis, the mechanical removal of the crystals from the ureters by ureteral catheterization and lavage may be necessary Decapsulation of the kidney has been tried with little or no success. In the author's experience, drug fever is the most baffling of the toxic manifestations because it is so difficult to know whether the fever indicates a reaction of the patient to his infection or to the drug

Clinical experience has proved that sulfadiazine is the sulfonamide of choice for systemic administration in surgical infections. However, its misuse and inadequately controlled administration in all types of infections, both diagnosed and undiagnosed, susceptible and nonsusceptible, have caused many unnecessary toxic reactions producing a false impression among some surgeons that it is too dangerous for practical use. We do not agree with this conclusion, and still

consider sulfadiazine to be a very valuable agent when it is used in proper dosage and under adequate laboratory controls Its correct use revolutionized the management of many infections, particularly those produced by the hemolytic streptococci and the pneumococci, and it also is of value in acute gonococcal lesions and certain mixed infections of the soft tissues and peritoneal cavity produced by various gram-negative and gram-positive bacteria of the intestinal tract. Its marked bacteriostatic action against mixed florae is often superior to that of penicillin in the usual concentrations which are built up in the blood during therapy. Its beneficial effect in actinomycosis is second only to that of penicillin.

After a considerable period of experimentation, it has been found that a dose of 0.1 gm. of sulfadiazine per kg of body weight in 24 hours divided into six doses at intervals of four hours will maintain a therapeutic level in the blood in most cases between 6 and 10 mg per cent For the average adult, 1.0 gm. every four to six hours is usually adequate. The dosage should be varied to insure a level in the blood between 6 and 10 mg. per cent. as measured by blood sulfonamide level determination.

Prophylactically, its systemic use in patients with contaminated wounds involving soft tissues or bone will prevent the development of spreading or invasive infection postoperatively in the great majority of instances, but there is no evidence that it will decrease the incidence of local infection. The topical use of sulfonamides is discouraged in this clinic. There is evidence that all of the sulfonamides act as foreign bodies when placed in wounds which are closed In penetrating wounds of the abdomen at the Cincinnati General Hospital, the preoperative and postoperative use of sulfadiazine has significantly reduced the percentage of deaths from 31.0 to 8.7. The use of sulfaguanidine, sulfasuxidine, or sulfathalidine preoperatively and sulfadiazine postoperatively has had a similar beneficial effect in gastro-intestinal resections

Certain disadvantages of sulfonamide therapy have limited its use, however. These disadvantages include. (1) the inactivation of its bacteriostatic activity by inhibitors found in pus, wound exudates, and necrotic tissue; (2) the existence of bacterial species and group resistance, (3) the inability to penetrate areas of pus and necrosis, (4) the development of drug-fastness by many of the infecting bacteria, (5) the occurrence of toxic reactions in some instances especially when its administration is not carefully controlled, and (6) occasional manifestations of drug idiosyncrasy.

It is obvious, therefore, that chemotherapy with the sulfonamides must be used as a valuable adjunct to well-established surgical principles and not as a means for displacing or violating them.

In most serious and mixed infections, the sulfonamides are used together with penicillin and streptomycin in order to achieve as broad a coverage as possible for the various bacteria, and to retard the development of acquired bacterial resistance, as advocated by Pulaski.

ANTIBIOTICS

Penicillin

With the introduction of penicillin, many of the therapeutic limitations of sulfonamide therapy were overcome. Of all the available chemotherapeutic agents,

prescribed, a similar toxic effect may occur. It is advisable, therefore, to determine whether or not a patient has previously had a toxic reaction during a course of therapy with one of these drugs Generally, it is advisable to keep patients who are receiving sulfonamide therapy out of the direct rays of the sun, and away from ultraviolet or infra-red radiation in order to prevent the complication of photosensitization.

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With the exception of acute leukopenia, the presence of most of the toxic manifestations of sulfanilamide or its derivatives which occur in the first two weeks of therapy usually can be suspected by careful clinical observation The physician should visit the patient receiving one of these drugs and should inquire as to his symptoms Headache, body aches, and malaise are often the precursors of many of the toxic reactions of sulfanilamide or its derivatives. Examinations should be made of the sclerae for congestion and jaundice, of the mucous membranes for pallor, and of the skin for rash. The temperature should always be taken to determine whether or not drug fever is present. Once crystals appear in a freshly voided specimen during sulfadiazine therapy, it is necessary to adopt vigorous measures to reduce the urinary concentrations of the drug This may be accomplished by reducing or withholding the compound until the crystals disappear, by forcing fluids, and by alkalinization of the urine to permit as much as a tenfold increase in the solubility of some sulfonamides The danger of sulfadiazine precipitation in the tubules of the kidneys or ureters may be minimized by knowledge of the fact that it occurs most frequently when the urine is acid and concentrated The forcing of fluids alone cannot be relied upon entirely to reduce the urinary concentrations of sulfonamides, and in fact this procedure may be contraindicated in patients with cardiac or renal impairment If urinary obstruction occurs from crystals, prompt action should be undertaken to prevent the development of uremia In addition to the increased fluid intake and administration of alkalis, the mechanical removal of the crystals from the ureters by ureteral catheterization and lavage may be necessary Decapsulation of the kidney has been tried with little or no success In the author's experience, drug fever is the most baffling of the toxic manifestations because it is so difficult to know whether the fever indicates a reaction of the patient to his infection or to the drug

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so that cell division did not take place, the bacteria were not killed by penicillin, but that they were killed when conditions were such as to permit cell division. These and other experiments indicated that the action of penicillin is either bacteriostatic or bactericidal, depending upon the existing conditions. It apparently inhibits the growth of organisms by interfering with their process of division.

TABLE I

PENICILLIN ACTIVITY *in Vitro* SENSITIVE MICRO-ORGANISMS

Gonococcus	*Clostridium botulinum*
Meningococcus	*Clostridium welchii*
Streptococcus	*Clostridium histolyticus*
hemolytic	*Clostridium septique*
viridans	*Clostridium sordelli*
micro-aerophilic	*Clostridium oedematiens*
anaerobic	*Clostridium sporogenes*
Staphylococcus	*Clostridium infermentans*
aureus	*Bacillus diphtheriae*
albus	*Bacillus pseudodiphtheriae*
anaerobic	Lactobacillus
Micrococci	*Crytococcus hominus*
Pneumococcus	*Spirillum minus*
Bacillus subtilis	*Streptobacillus moniliformis*
Bacillus anthraxis	*Treponema pallidum*
Actinomyces bovis	*Bacillus alkaligenes* (some strains)
Clostridium tetani	*Leptospira icterhemorrhagiae*
Clostridium tetanomorphum	*Erysipelothrix rhusiopathiae*

TABLE II

PENICILLIN ACTIVITY *in Vitro*: RESISTANT OR SLIGHTLY SUSCEPTIBLE STRAINS OR MICRO-ORGANISMS

Bacillus coli	*Acna bacillus*
H. influenzae	*M. tuberculosis*
Bacillus typhosus	*Bacillus tularense*
Bacillus paratyphosus	*Brucella melitensis*
Bacillus dysenteriae	*Brucella abortus*
Bacillus proteus	*Bacillus melaninogenicum*
Bacillus enteritidis	*Monilia albicans*
Bacillus pyocyaneus	*Monilia candida*
Aerobacter aerogenes	Blastomyces
Bacillus fluorescens	Toxoplasma
Bacillus friedländeri	*Bacillus mycoides*
Bacillus prodigiosus	Lymphopathia venereum virus
Bacillus pestis	
Vibrio cholerae	

It has only slight action on spores and little effect on organisms in the resting phase. No detectable amount of penicillin is destroyed or absorbed from solution by the bacteria. The action of penicillin is not controlled by the number of bacteria present and there is a considerable lag phase. In this respect, penicillin action resembles that of an enzyme rather than that of a compound which is used up during the production of its physiologic effect.

The action of penicillin is not inhibited by blood, pus, split protein products, or para-aminobenzoic acid as is that of the sulfonamides. Cavallito, Bailey, and others discussed the relationship of sulfhydryl groups to the activity of penicillin

penicillin most nearly approaches the ideal. When its chemical structure was determined, five compounds of penicillin were described: penicillin G, penicillin X, penicillin F, dihydro F penicillin, and penicillin K. The formula proposed for penicillin is $C_9H_{11}O_4$ SN-R. The *R* group varies with the penicillin species as follows

Δ_2 pentenyl in penicillin F
N-amyl in penicillin dihydro F
benzyl in penicillin G
p-hydroxy in penicillin X
n-heptyl in penicillin K

Other species have been reported such as S_1, S_2, S_3 which are absorbed on the chromatograph near penicillin X, and other F and K types have been described. Commercial preparations of penicillin are mainly mixtures of sodium, potassium, calcium, or procaine salts of one or more of the five principal penicillins, but predominantly penicillin G.

Penicillin preparations in general lose activity rapidly on exposure to air or heat. They are unstable when treated with acids, alkalis, alcohol, heavy metals, or oxidizing agents The stability of the different types of penicillin in the order of decreasing stability are G, X, F, and K. The penicillins are strong monobasic acids which are soluble in ether, acetone, alcohol, ethyl acetate, amyl acetate, cyclohexane, and dioxane

Penicillin has an extensive antibacterial spectrum which is illustrated in Tables I and II

The precise manner of its action within the body is not known. Hobby and Dawson in 1944 showed that conditions which stimulated the rate of growth of susceptible bacteria increased the rate at which penicillin acted. Conversely, conditions which retarded the rate of growth of bacteria also decreased the rate at which penicillin acted. Penicillin was found to be most effective when active multiplication was taking place. They also demonstrated that sulfadiazine alone had no effect on the rate of growth of hemolytic streptococci during the first five to seven hours of incubation During the same period of time, penicillin destroyed about 90 per cent of the organisms originally present. When incubation was continued further, penicillin gradually destroyed the remaining viable organisms. Todd demonstrated that there was a relationship between penicillin's bactericidal properties and its ability to lyse bacteria. He pointed out that bacteriostasis or even death to the organisms could be produced without lysis, and he interpreted the entire phenomenon as being part of one continuous chain of action in which bacterial multiplication, death, and then lysis were effected progressively by the same mechanism He pointed out, as had Hobby and Dawson, that penicillin was much more effective in young cultures when active multiplication was going on, and that the actively multiplying bacteria were more susceptible to its lytic action than the older ones. Rantz and Kirby also believed penicillin [illegible] bactericidal action is exerted only [illegible] divide. Similar opinions have been [illegible] associates observed that if the temperature of a culture of penicillin-susceptible bacteria was made low enough

to penicillin of a wide variety of penicillinase-producing organisms (Abraham and Chain; Altemeier) was related to the speed with which they produced the enzyme rather than to the amount of it which they produced. Although production of this enzyme may increase the resistance of gram-negative bacteria, they concluded that it was not the primary factor in their resistance to penicillin.

Methods of Administration. If administered in the form of the sodium, potassium or calcium salt, penicillin is readily absorbed when given intramuscularly or intravenously, and it is largely excreted in the urine. If given intravenously, it is rapidly eliminated by the kidneys through which most of it passes unchanged. It can be recovered from the urine and used again. That which cannot be recovered disappears in the body. Peak concentrations are reached in the blood within a few minutes, and then the blood level begins to fall precipitously. Following intramuscular injection, maximal concentrations are reached in from 15 to 30 minutes, and the blood levels are more sustained. Subcutaneous injections produced a more variable and less reliable rate of absorption, but peak concentrations are generally reached in about 60 minutes. If renal function is normal, only traces of penicillin may be found in the blood three or four hours after its injection. Penicillin is readily absorbed from the duodenum, but unless properly buffered, it is rapidly destroyed by the acid reaction of the stomach when taken by mouth. The absorption of penicillin from the rectum is poor, and absorption from the intestine is greatest following duodenal administration which produces a maximum blood plasma level in 15 to 30 minutes with a curve similar to that obtained by intramuscular injection. When injected into infected bursae, joints, pleural cavities, or intrathecal spaces, its absorption is delayed and appreciable amounts of penicillin may remain in such cavities 20 to 36 hours after injection. Penicillin may also be absorbed rapidly by inhalation. Its presence can be determined in the blood by standard tests on staphylococci or *B. subtilis*. If administered intramuscularly or intravenously, it does not readily enter the spinal fluid

After its absorption in the blood stream, penicillin combines either chemically or physically with the albumin fraction of plasma proteins, and forms a therapeutically active combination. Thence it diffuses into the various tissues, but its diffusion into the spinal fluid is slow and ineffective.

It passes slowly into synovial, pleural, and pericardial fluids, but diffuses readily into ascitic fluids in which it reaches concentrations comparable to those in the blood It passes from maternal to fetal blood with ease and is found in detectable quantities in the amniotic fluid. It does not pass readily into the vitreous or aqueous humors nor into pus within abscesses. It is not destroyed by the liver.

If renal function is normal, penicillin is rapidly excreted by the kidney and within a few hours after a single dose, 50 to 90 per cent of the antibacterial agent may be recovered from the urine. It is also excreted in bile and a small amount is probably excreted in the stool Little if any penicillin is excreted in saliva, sweat, milk, or tears Patients with cardiac failure or impaired renal function have retarded excretion of penicillin. The threshold of toxicity of penicillin as yet has not been demonstrated We have frequently found it necessary to use 1,000,000 units of penicillin every three hours, and in one instance, a child received 100,-000,000 units every 24 hours for two weeks without evidence of toxicity. Toxic reactions from excessive blood levels in human beings have not been reported.

and have shown that various materials which contain this group are able to inactivate the antibiotic substance

In 1946, Hobby and Dawson concluded as the result of experiments that the combination of penicillin and sulfadiazine produced at times a greater bacteriostatic effect *in vitro* than the same concentration of sulfadiazine or penicillin alone Massell, Meyserian, and Jones showed that sulfonamide drugs used *in vitro* with penicillin reduced the minimal effective concentration of penicillin for strains of the *Streptococcus viridans*. This was substantiated by Bigger.

Hobby, in 1944, and Altemeier showed that penicillin exerted an antibacterial action against gram-negative as well as gram-positive bacteria, but that this property of penicillin became more apparent in high potency preparations. It was suggested that a form of penicillin showing a greater activity against gram-negative organisms may exist.

Reports have been made of penicillin-fastness being acquired by hemolytic staphylococci, streptococci, pneumococci, gonococci, and probably many others Spink and his associates have shown that staphylococci may become resistant to penicillin, although they did not believe that this had much clinical importance There was no reason to believe that the mechanism involved in the development of penicillin resistance was the same as in the case of resistance to sulfa compounds

McKee and Houck reported that increased resistance to penicillin and loss of bacterial virulence were accompanied by a slowing in the rate of growth of the organisms and variations in the types of colonies Of clinical importance in penicillin therapy is the question of whether *in vitro* resistance to the antibiotic is indicative of resistance *in vivo* Warmer and Amluxen reported that a hemolytic *Staphylococcus aureus* which was resistant to penicillin *in vitro* resisted the same concentrations *in vivo* Similar observations have been reported by Schmidt and Sesler for pneumococci, and would seem to be generally applicable.

The prevention of the development of penicillin-fast strains of pathogenic bacteria by the use of adequate dosage schedules is extremely important if penicillin therapy is to continue as highly successful as it is at present. If penicillin-fastness develops, it apparently may persist over prolonged periods of time, although this again is influenced greatly by the characteristics of the specific strain There is also a marked difference between strains of the same type of organism as regards the ease with which such fastness can be developed.

Miller, Scott, and Moeller reported peculiar morphologic changes in gonococcal smears observed at the time the numbers were diminishing most rapidly under the effect of penicillin Gardner also noticed morphologic changes in bacteria exposed to penicillin, which were best shown when the concentration of penicillin was too low to inhibit growth completely *Clostridium welchii*, when grown in fluid media with a somewhat inadequate concentration of penicillin, showed extreme elongation of the majority of its cells

Penicillin is not antitoxic, Neter and Wil, and Altemeier, Logan, Tytell, and Tytell showed that tetanus toxin which had been mixed with penicillin was as toxic for mice as was the toxin alone.

Dietz and Bondi showed that sodium azide rendered penicillinase-producing organisms more susceptible to penicillin. They also showed that the susceptibility

the absorption of water-soluble penicillin is retarded by the added beeswax, pectin, or aluminum monostearate, and effective blood levels for 24 or more hours can be maintained with single daily injections in the majority of cases. Objections to the oil and beeswax suspensions of penicillin include pain, local reactions, retained residue after absorption of the chemotherapeutic agent, and occasionally granuloma developing at the site of injection.

Delayed absorption has also been made possible by the injection of insoluble salts such as procaine penicillin and the heavy metal salts of penicillin. Procaine penicillin may be suspended either in aqueous solution or oil, and a single injection of 300,000 units every 24 hours will produce satisfactory chemotherapeutic levels for susceptible bacteria for 24 hours in practically all cases, and for as long as 48 hours in many of them.

Crystalline procaine penicillin G in oil or aqueous suspension is gradually replacing penicillin in oil and wax, since it possesses fewer disadvantages and can be successfully used in most susceptible infections. Procaine penicillin G is heat-stable, requires no refrigeration, and flows freely at room temperature, thus requiring no preliminary warming. Two per cent aluminum monostearate has usually been added to procaine penicillin G in peanut oil suspension as a delaying agent. The addition of aluminum monostearate permits a prolonged plateau-like level for 48 or more hours in all subjects. Occasionally levels of 96 hours have been produced, but they cannot be relied on, in our experience, beyond 48 hours. The aluminum monostearate also minimizes settling of the insoluble procaine penicillin salt. Within the tissues, the procaine penicillin molecule releases its contained procaine which is rather quickly destroyed, chiefly by the liver. Presence of procaine, however, serves to make the injection virtually painless because of its local anesthetic properties.

One of our objections to the repository preparations of penicillin has been the relatively low concentrations of penicillin maintained within the circulating blood, levels of from .15 to .03 units per cubic centimeter being obtained. Consequently it has been our practice to use supplementary injections of 100,000 units of aqueous penicillin intramuscularly every eight or 12 hours when using the repository forms in severe or relatively resistant infections. Recently commercial preparations have been introduced which contain both procaine penicillin and sodium penicillin in a product which can be easily and satisfactorily suspended in aqueous solution. We have tested these products carefully and find that much higher levels are produced initially and maintained throughout the 24-hour period (Fig. 1). Other advantages include ease of suspension, ease of injection without plugging of syringes or needle, and minimal pain at the site of injection.

The retarded excretion of penicillin has been produced by the oral administration of caronamide in doses of 3 gm. every four hours for a period of two to 19 days. This may be used to decrease the interval between injections of aqueous penicillin, to enhance the blood levels from two *to seven times*, or to decrease the amount of penicillin necessary for therapy of a given case. Two of its disadvantages are the large daily doses required and the fact that nausea is produced in some instances.

The oral administration of penicillin has been used effectively in selected cases,

In therapeutic doses, penicillin does not injure leukocytes or interfere with cellular growth of tissues. The chief toxic manifestations so far observed have been due to sensitization such as urticarial rashes, exfoliative dermatitis, drug fever, etc.

Skin reactions are noted in the course of aqueous penicillin therapy in 5 per cent of the cases, and in 7 per cent of those receiving penicillin in oil and beeswax. Individuals who have suffered from pre-existing eczematoid dermatitis have reaction rates to penicillin as high as 50 per cent. The eruption may be maculopapular, vesicular, or even bullous in type Erythema multiforme or nodosum may occur. The eruption may be localized as in contact dermatitis or it may be severe, generalized, or exfoliative. In urticarial eruptions in adults, the concomitant administration of benedryl or pyribenzamine in dosages of 150 to 200 mg. per day may permit the continuation of penicillin therapy or will relieve the urticarial eruption after the withdrawal of penicillin

Neurologic disturbances may result from the direct effect of penicillin upon the central nervous system under certain conditions, and reports of transverse myelitis and peripheral nerve palsies have appeared.

Dosage and Dosage Schedules It is difficult to determine adequate penicillin dosages but, in general, the trend has been toward larger doses Staphylococcal infections usually require a higher dosage than streptococcal infections, and gonococcal the lowest Doses of penicillin may vary with different patients, the nature of the infection, and the method of administration. In the average severe staphylococcal or streptococcal infection, with or without bacteremia, intramuscular doses of 15,000 to 25,000 units every three hours have produced excellent results, but the requirements of each case may be different In severe or fulminating infections, the dose may be increased to 50,000 to 100,000 or more units every two or three hours In resistant or mixed infections, as much as 500,000 to 1,000,000 or more units may be given every three hours. When massive doses are given, it is usually necessary to give the injections intravenously because of the larger quantities of diluent required and the patient's discomfort when this amount is given intramuscularly Since penicillin does not penetrate the subarachnoid spaces in adequate bacteriostatic amounts, supplementary daily injections of 10,000 units are generally considered necessary in infections of the meninges Whenever possible, the causative organism should be determined and tested against penicillin *in vitro* to determine its sensitivity.

Originally the dosage schedules devised for the therapy of susceptible surgical infections were based upon the assumed necessity of maintaining a therapeutic concentration of this agent in the tissues and circulating blood The effectiveness of the numerous methods of administration based upon this concept has been well established However, disadvantages of the continuous or three-hourly injection of penicillin and the need to extend the usefulness of this agent have led to an almost continuous search for some preparation which would produce effective control of an infection when administered only once every one to four days Three plans have been devised to overcome these disadvantages: delayed absorption, delayed excretion, and oral administration

Delayed absorption has been accomplished with suspensions of soluble penicillin in oil or insoluble salts of penicillin in oil or water With the preparations in oil,

similar to that which we had learned from previous experience to expect. It is not recommended in severe, fulminating, or mixed infections.

As in the case of sulfadiazine, parenteral penicillin given prophylactically has attenuated or localized infections developing within contaminated wounds. Since the hemolytic staphylococcus is the most frequent cause of wound infection, we consider penicillin superior to the sulfonamides for this purpose. This effective control of postoperative infections has made possible successful operative ven-

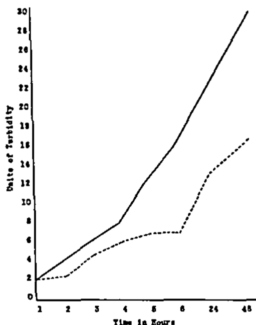


FIG 2.—Chart illustrating the persistence of the bacteriostatic effect of penicillin on the hemolytic streptococcus after a four-hour exposure to 2 units of penicillin per cc.
——— No exposure to penicillin
- - - - - - Four-hour exposure to penicillin

tures of greater scope, particularly in the thorax, and has thereby greatly stimulated advancement in surgical technics.

In the treatment of many established surgical infections, particularly those caused by staphylococci, aerobic and anaerobic streptococci, gonococci, actinomyces, and the Clostridia of gas gangrene, penicillin is still the most effective chemotherapeutic agent available. Evidence of its superiority in the therapy of staphylococcal infections is overwhelming, and it has replaced all previous forms of therapy in such lesions. Frequently penicillin has so controlled the invasive qualities of staphylococcal infections that emergency radical surgical decompression or excision of infected areas has been eliminated or replaced by more conservative types of surgery Its value has been outstanding in those infections caused by sulfonamide-resistant strains of the streptococcus and gonococcus

Since the great majority of infections treated by surgeons is caused by the staphylococcus, streptococcus, and gonococcus, penicillin has been of tremendous value to the surgeon. The early treatment of diffuse infections caused by any of these micro-organisms may be followed by such prompt and complete arrest of the destructive bacterial process that suppuration does not develop and surgical

providing it has been buffered and the dose has been at least five times greater than that which would have been given parenterally. Within its scope of application, it has been particularly useful in the therapy of ambulatory patients

Considerable evidence has been accumulated to show that the bacteriostatic effect of penicillin persists for a considerable length of time after its disappear-

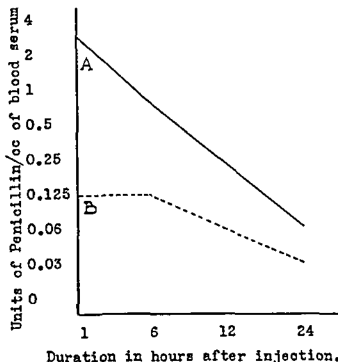


FIG 1—A comparison of the height and duration of the penicillin blood levels produced by a single intramuscular injection of (A) mixture of 300,000 units of procaine penicillin G and 100,000 units of sodium penicillin G in aqueous suspension (B) 300,000 units of procaine penicillin G only

ance from the blood, and that it is not necessary to maintain a bacteriostatic concentration within the blood (Fig 2)

The results of Tillett and his associates in 1944 suggested that the antibacterial effects of penicillin on invasive pneumococci inhibited their growth for a considerable period after blood concentrations were no longer detectable. When injections were made every 12 to 16 hours, the results in a small number of cases seemed to be just as satisfactory as those obtained with more frequent injections Similar inhibitory effects on streptococci infecting mice for eight or more hours were suggested by the study of Jawetz in 1946 The investigations of Zubrod in hemolytic streptococcic infections in mice also indicated that the interval between doses of an aqueous solution of penicillin could be extended considerably beyond four hours

During the past 15 months, we have treated over 250 selected cases of established surgical infections with intramuscular injections of 100,000 to 200,000 units every eight to 12 hours The clinical results obtained in patients with susceptible infections of moderate severity were gratifying and the pattern of response was

antibiotic agent to accumulate in dangerous amounts in the blood. In the body, the streptomycin is distributed apparently only in the extracellular water, and it does not pass readily into red blood cells or the pus of walled-off abscesses. It diffuses so slowly into the spinal fluid after parenteral injection that detectable amounts cannot be found. On the other hand, in frank meningitis, easily detectable amounts have been found in the spinal fluid. This antibiotic passes over slowly into pleural, synovial, and pericardial effusions, but it passes easily into normal peritoneal fluid or into the exudate of peritonitis. Adequate concentrations of streptomycin following its intramuscular injection have been noted in the aqueous and vitreous humors of the eye. This antibiotic diffuses into fetal blood and amniotic fluid in concentrations of about half of those found in the maternal blood.

Determinations of the blood levels produced by intramuscular injection of streptomycin give the following information: If 0.1 gm. of streptomycin is given to an average adult patient every three hours, the mean concentration maintained in the blood will be 2 to 3 micrograms per cubic centimeter during a three-hour period. If 0.2 gm. is given, the mean concentration will be twice as great. In general, for each dosage increment of 0.1 gm. given every three hours, the mean concentration of streptomycin in the circulating blood is increased 2 to 3 micrograms per cubic centimeter. The intramuscular route of administration is the most useful, and a dose of 1 to 2 gm per day in divided doses will usually be adequate. When given by mouth, streptomycin is absorbed only slightly, but it reduces the count of gram-negative bacteria in the stool to a very low figure. Large doses, 2 to 4 gm. per day, may occasionally be required.

Flippin and Rhoades have demonstrated that after the injection of 0.6 gm. of streptomycin intravenously, concentrations of streptomycin in the urine may reach levels between 16 and 520 micrograms per cubic centimeter over a 12-hour period.

Dosage. There are many problems concerned with the adequate dosage of streptomycin for a given case, which include the species of infecting microorganism, its sensitivity to streptomycin, the presence of bacteremia, the anatomic location of the infection, and the weight and age of the patient. Bacterial susceptibility to the action of streptomycin varies widely. Because of the wide range in sensitivity, it is important that each infecting organism should be tested before treatment and the dosage planned accordingly. It is desirable to use the amount of streptomycin which will produce a concentration in the blood tissues sufficient to inhibit the growth of the infecting organism. The maintenance of a concentration of streptomycin in the blood stream four to eight times that found to be necessary to inhibit completely the organisms *in vitro* is recommended. Unfortunately, many organisms develop marked resistance *in vivo* to large concentrations of streptomycin often within four to ten days after the start of treatment. Another important feature of streptomycin therapy is the so-called stimulating effect of streptomycin on the growth of bacteria. The experimental studies of Welch, Price, and Randolph have shown that streptomycin at certain concentrations in mice infected with *E. typhosa* actually increased the fatality rate. If large doses were given, all of the animals were protected.

Toxicity Histamine-like effects such as headache, flushing of the skin, nausea, and vomiting were formerly seen but rarely occur now with the more purified

intervention does not become necessary. In the treatment of suppurating surgical infections caused by these bacteria, penicillin therapy has had a striking beneficial effect on mortality and morbidity but the fundamental surgical principles of early, accurate diagnosis, early treatment, rest, adequate external drainage, and general supportive treatment remain as important as ever

STREPTOMYCIN

Streptomycin is a basic organic compound first isolated in 1942 from *Streptomyces griseus* It is of moderate molecular size, and its chemical formula is $C_{21}H_{39}N_7O_{12}$. It is soluble in water but insoluble in organic solvents. It is also hygroscopic When kept dry and at room temperature (25° C.) streptomycin remains stable for six months to one year. Its aqueous solution, however, should be refrigerated. It has a selective antibacterial action against gram-negative bacteria as does streptothricin, but it is considerably less toxic Streptomycin acts, therefore, on such gram-negative bacteria such as Eberthella, Salmonella, *Escherichia, Shigella, Klebsiella, Brucella, Pasteurella, and the Proteus group*

TABLE III

STREPTOMYCIN ACTIVITY IN VITRO
SENSITIVE MICRO-ORGANISMS

B coli	*Br abortus*
A aerogenes	*Br melitensis*
B typhosus	*B subtilis*
B paratyphosus	Other gram-positive sporulating aerobes
B pyocyaneus	
P tularensis	Streptococci
B. proteus	Staphylococci
K pneumoniae	*M tuberculosis*
H influenzae	*M phlei*
H pertussis	Actinomyces

Considerable resistance is shown by some strains of Pseudomonas, however Sensitivity to streptomycin is also shown by numerous gram-positive organisms such as Staphylococci, hemolytic Streptococci, and pneumococci, whereas resistance is exhibited by all members of the spore-forming anaerobic group

There are three principle routes of administration intramuscular, subcutaneous, and topical, which also includes intrathecal, intraperitoneal, and intrapleural Streptomycin can be administered only by the parenteral route for the treatment of systemic infections. When administered by mouth, practically no streptomycin is absorbed into the blood and the bulk of the dose is excreted in the stool. Little or none is absorbed Following the intravenous injection of streptomycin, maximal concentrations in the blood occur at the end of the injection After intramuscular injection, there is a gradual rise with highest levels being found in the blood within 60 to 120 minutes Thereafter, the levels may fall rapidly and only small amounts are found in the blood four hours later. Two hours following intramuscular or intravenous injection, the excretion of streptomycin by the kidneys is greatest Within 12 hours, from 30 to 60 per cent may be excreted in the urine in the presence of normal renal function. When renal function is seriously impaired, the rate of excretion of streptomycin may be decreased, permitting the

the urine. Elevation of the blood urea nitrogen should be watched for. Pre-existing renal impairment will interfere with excretion of streptomycin, thereby producing unusually high blood levels and increasing the risk of toxicity.

Recently, *dihydrostreptomycin* has been derived from streptomycin and it is conspicuously less neurotoxic. Because of this, it may be more safely administered in larger daily doses, larger total doses, and for longer periods of time than has been possible with streptomycin. When daily doses of streptomycin have been limited to 1 or 2 gm., dihydrostreptomycin may be used in doses of 2 to 3 gm. daily. Daily doses of 2 gm. of dihydrostreptomycin intramuscularly may be well tolerated for as long as four months, and it is apparently possible to give as much as 2 gm. daily over periods of 60 to 90 days without serious risk of neurotoxicity in the majority of patients. In addition, hypersensitivity reactions and renal complications appear to be less frequent, and many patients who have been unable to continue streptomycin therapy have been able to tolerate dihydrostreptomycin. Unfortunately, resistant strains of bacteria appear to develop as rapidly as with streptomycin. *In vitro* studies indicate that dihydrostreptomycin has an antibacterial spectrum parallel with that of streptomycin.

The clinical therapeutic indications for streptomycin therapy in surgery include bacteremias caused by gram-negative bacilli, meningitis produced by gram-negative bacilli, acute and chronic urinary tract infections, liver abscesses, cholangitis, secondary peritonitis, pyelophlebitis, abscesses of the liver, mixed infections of wounds, and tuberculosis. Clinical results in cases of bacteremia, urinary tract infections, and cholangitis have been encouraging, but questionable in secondary peritonitis, liver abscess, and pyelophlebitis.

The drug is effective in controlling infections of the urinary tract produced by gram-negative bacteria. Under such circumstances it is desirable to control the dosage by determining the susceptibility of the infecting organism and adjusting the dosage accordingly Bacteremia in infections of the urinary tract due to *B. coli* have also responded satisfactorily to streptomycin. Other beneficial results have been obtained in cases of bacteremia and infections of the urinary tract caused by *B. proteus* and *A aerogenes*. Success depends largely upon the use of sufficient doses from the beginning to produce a maximum effect, and upon early surgical drainage of abscesses or distributing foci before the development of bacterial resistance. In chronic infection, the response may be excellent temporarily, but failure to correct any physical factors predisposing to or associated with the infection may result in relapse or recurrence.

Clinical experience has indicated that streptomycin is of definite value in the treatment of tuberculous infections. Patients with early exudative and hematogenous forms unquestionably have received some benefit from prolonged periods of therapy. Lesions of recent development showed prompt regression but chronic areas with walled off and encapsulated lesions responded relatively poorly. Because of its significantly less neurotoxic effect, dihydrostreptomycin is preferable to streptomycin in the treatment of tuberculous lesions.

In tuberculosis, the use of antibiotic agents is an adjunct but not a substitute for rest, collapse therapy, surgery, and other standard measures. Nevertheless, streptomycin can exert an impressive effect on the course of tuberculosis and is the agent of choice for this purpose. In tuberculous meningitis, high dosages are

preparations *Nevertheless, streptomycin may produce definite toxic manifestations* in about 6 per cent of all patients to whom it is administered for any considerable period of time. The shorter the period of therapy, the less numerous will be the toxic reactions observed. Local reactions at the site of injection may occur, including pain, soreness, redness, and induration. If pain occurs, it usually may be reduced by the injection of 2 per cent procaine hydrochloride with the streptomycin There is no evidence that procaine inactivates the streptomycin. Sensitization reactions are characterized by skin eruptions, fever, and eosinophilia. The fever may appear on the third day or later, and may be mild, hectic, or maintained. Eosinophilia up to 10 to 15 per cent has been observed The rash may be erythematous, urticarial, maculopapular, and even hemorrhagic The eruptions may be localized or generalized In some instances, an exfoliative dermatitis has occurred, usually appearing on the third to the tenth day of treatment, although it may be seen as early as the second day or as late as 10 days after treatment has been stopped The eruptions may persist one to nine days, the average being about four Contact dermatitis may occur in physicians and nurses who prepare and administer streptomycin.

The most serious toxic manifestation is streptomycin's direct neurotoxic effect on the eighth cranial nerve. It has been noted as early as the seventh or eighth day of treatment, and it occurred in about 1 per cent of patients who received streptomycin over a period of time in excess of 21 days in one series, and in 96 per cent in another series when treatment was prolonged over a period of several months The auditory or vestibular mechanism may be affected, and vertigo and tinnitus are the presenting symptoms. Vertigo may be a serious symptom in *patients receiving prolonged streptomycin treatment. Apparently there is some* interference with vestibular function in all patients receiving large doses of streptomycin over a long period of time, and although many did not complain of vertigo, hypo-active reflexes were found in the vast majority of patients when caloric stimulation of the vestibular apparatus was tested before and during treatment. The disability may become so severe in a patient that walking without assistance may be impossible. Clinical recovery following discontinuance of therapy has been slow. When the administration of streptomycin for a long period of time is anticipated, it is advisable to have the patient's hearing tested with an audiometer before therapy is commenced and at frequent intervals thereafter. Caloric stimulation tests also should be made before treatment and at periods of two weeks. The occurrence of diminished auditory acuity, tinnitus, vertigo, or any disturbance of function of the vestibular apparatus detected by caloric stimulation should be an indication for the immediate discontinuation of streptomycin therapy

Other neurologic disturbances observed following streptomycin treatment have been diplopia, nausea, anorexia, and paresthesia about the face and extremities. Beham and Perr reported 3 cases of painful stomatitis developing in patients treated with streptomycin. In certain animal species, streptomycin leads to fatty infiltration of the liver and kidneys which appears to be reversible if administration is discontinued. It has not been reported in humans under treatment with streptomycin Renal irritation may be noted in patients receiving streptomycin, as evidenced by the appearance of albumin and occasionally red blood cells in

on the third to fifth day as evidenced by albuminuria, hematuria, and formation of casts and azotemia. In some instances, the albuminuria may be transient, disappearing while the patient is under therapy. Pulaski reported a high incidence of nephrotoxic phenomena in a series of patients and animals treated with bacitracin.

In addition, pain, redness, heat, and induration at the site of injection may occur. The local reaction may appear immediately after the injection, or may be delayed for 12 or more hours. General malaise associated with nausea and anorexia has been observed occasionally. Some lots of bacitracin have shown more toxicity than others. Bacitracin is being thoroughly studied to demonstrate the nature of the residual toxic elements. Studies are being carried out in an effort to separate the toxic factors from bacitracin or to nullify their toxic action. The systemic administration of bacitracin by intramuscular or subcutaneous injection is at present under clinical investigation in patients at New York, Philadelphia, New Orleans, and Cincinnati in order to demonstrate the further indications and limitations of this new antibiotic in the treatment of infections. The initial dose recommended at present is 10,000 units every six hours given intramuscularly for 48 to 72 hours. If no signs of nephrotoxicity develop within this time, the dose may be increased at 15,000, 20,000, or 30,000 units every six hours. Bacitracin should not be given more often than once every six hours. Because of the pain produced locally at the site of injection, bacitracin should be administered intramuscularly in a solution of 2 per cent novocain in physiologic saline

The clinical indications are essentially the same as those for penicillin. There was an over-all favorable response reported by Meleney et al. in about 70 per cent of the cases of susceptible established infections treated with bacitracin. In the treatment of extensive and progressive bacterial synergistic gangrene, syphilis, and penicillin- and streptomycin-resistant infections, bacitracin has been of particular value It has been administered orally for infections produced by *Endamoeba histolytica* with success. Greater refinement and a means of eliminating the nephrotoxic factors of bacitracin are necessary before the drug will be acceptable for widespread clinical use.

Aerosporin (Polymixon B)

Aerosporin is an antibiotic produced by the *Bacillus aerosporus* greer. Aerosporin is somewhat more toxic than streptomycin, but its antibacterial efficiencies for gram-negative bacteria are similar. It was shown to be effective for a wide variety of gram-negative bacteria including *H. influenzae*, *H. pertussis*, *E. typhosa*, *B coli*, *M catarrhalis*, Salmonella, *A. aerogenes*, *Vibrio cholerae*, *B pestis*, *Streptococcus enteriditis*, and *Pseudomonas pyocyaneas* by Stansley, Shephard, and White One distinct advantage of aerosporin is the lack of resistance developed by strains subjected to its action; a factor which is in sharp contrast with streptomycin Aerosporin is readily produced, is relatively stable, and in addition to its selective action is of high intrinsic potency. Weight for weight it has essentially the same order of chemotherapeutic activity against gram-negative organisms as penicillin has against gram-positive It is unique as a chemotherapeutic agent in its remarkable specificity for gram-negative bacteria, thus distinguishing it from all other antibiotics reported. In experimental

necessary over particularly long periods and it has been estimated that the use of dihydrostreptomycin in sufficient dosage will result in recoveries in 10 to 15 per cent of these patients. An additional 10 per cent will probably survive but be in poor condition Disseminated hematogenous tuberculous infections of the miliary type have responded to streptomycin, complete clinical and roentgenographic remission occurring in a large proportion of the cases after prolonged treatment. *In tuberculosis of the tracheal, bronchial, or laryngeal mucous membranes,* good results have been obtained. In renal tuberculosis improvement may follow the use of streptomycin, but the ultimate outcome has been doubtful.

In general, the factors which may cause failure in the treatment of streptomycin-susceptible infections of all types include inadequate dosage, acquired resistance by the infecting bacteria *in vivo,* failure to use surgery at the proper time, and localization of the process in areas inaccessible to streptomycin or surgery.

BACITRACIN

This is an antibiotic derived from the Tracey strain of *Bacillus subtilis* and it is neutral, water-soluble, and relatively heat-stable. Its distribution for parenteral use is still on allocation for experimental use. Bacitracin's antibacterial spectrum *is extensive and similar to that of penicillin It is effective against most strains* of hemolytic streptococci, nonhemolytic streptococci, coagulase-positive staphylococci, pneumococci, gonococci, anaerobic cocci in general, Clostridia, *Bacillus diphtheriae, Bacillus pseudodiphtheriae, Treponema pallidum,* the spirochetes of the mouth, the actinomyces group of organisms, and the *Endamoeba histolytica* It has little or no action against the large group of aerobic, gram-negative, nonsporulating bacilli Bacteria show but moderate tendency to build up resistance to the compound, either *in vitro* or *in vivo,* and blood, pus, or necrotic tissue does not destroy its action. Bacitracin's action is similar in certain respects to that of penicillin It differs, however, from penicillin in that its bactericidal activity appears to be directly proportional to its concentration.

The chief advantages of bacitracin over penicillin are: (1) It is not inhibited by the organisms which produce penicillinase, (2) *it is more slowly eliminated* from the body and therefore can be given at greater intervals; (3) its effectiveness [illegible] tendency [illegible] effect with [illegible] against many penicillin-resistant infections Its chief disadvantage as compared with penicillin is that it has not yet been obtained in a pure crystalline form and in the present stage of its impurity, it produces, when injected systemically in man, certain evidence of nephrotoxicity which limits its dosage, its scope of action, and the duration of treatment Its chief advantages over streptomycin are its wider antibacterial spectrum, particularly with regard to the anaerobic bacteria, and the low incidence and degree of resistance which develops during the course of treatment Its chief disadvantage with respect to streptomycin is its ineffectiveness against the gram-negative, aerobic, nonsporulating bacilli. When used topically, it has been found to be effective and nontoxic When used parenterally in humans, it is readily absorbed and diffused throughout the tissues in a manner similar to penicillin After parenteral administration, signs of nephrotoxicity may occur

except for occasional nausea and vomiting. No reports of anemia, jaundice, azotemia, drug fever, or agranulocytosis have been published.

Aureomycin can be administered orally to produce effective antibacterial levels in the blood and tissues. It is excreted by the kidneys, and concentrations of the agent may be developed in the urine as high as 256 micrograms per cubic centimeter in two to 16 hours after dosage. The dose is 100 to 250 mg. every one to four hours, although it may be varied in amount, interval, and duration.

It is indicated in the treatment of many gram-positive and gram-negative infections, as well as in various rickettsial and virus infections. Its full clinical potentialities are still undetermined. Aureomycin is equal to streptomycin in the treatment of gram-negative infections, and apparently superior in the therapy of urinary tract infections. It is less effective than penicillin but more effective than streptomycin in the treatment of gram-positive bacterial infections. It is of value in the treatment of rickettsial and virus infection, including atypical pneumonia. It will be a valuable addition to the field of chemotherapy.

Chloromycetin

Chloromycetin is a new antibiotic agent of unusually great promise, is derived from *Streptomyces venezuelae* and its antibacterial activity is similar in many respects to that of aureomycin. The facts that Rebstock has been able to synthesize chloromycetin and Long and Troutman have devised a method for its commercial production on a large scale are of great practical significance. Its antimicrobial spectrum includes various gram-negative bacilli such as *B. coli*, *A. aerogenes*, *B. typhosus*, *B. dysenteriae*, and *B proteus* as well as many other gram-negative bacteria; gram-positive pyogenic cocci; the Clostridia of gas gangrene; and various viruses and rickettsiae. It is readily absorbed after oral administration and adequate levels are produced in the blood and tissues.

Its particular value in typhoid fever, epidemic typhus, undulant fever, bacillary dysenteries, Rocky Mountain spotted fever, psittacosis, virus or atypical pneumonia, and urinary tract infections is being established by various clinical investigations at the present time Our studies of surgical gram-negative bacterial infections and lymphopathia venereum indicate that chloromycetin is more effective in their management than other agents. Chloromycetin promises to be a valuable addition to the field of chemotherapy It has little activity against the tubercle bacillus and less against gram-positive cocci. It is more effective than streptomycin against some gram-negative bacterial infections but less effective in tuberculosis In the treatment of gram-positive infections, it has been surprisingly effective, particularly in those caused by penicillin-resistant bacteria.

The following antibiotic agents apparently do not have great clinical potentialities in the treatment of human infections, but they are discussed very briefly for the sake of completeness.

Pyocyanase and Pyocyanine

Pyocyanase is the oldest example of a known micro-organism producing an antibacterial or antagonistic substance for other bacteria. It was named pyocyanase by Emmerich and Loew in 1899, who thought that it was an enzyme.

infections produced by gram-negative bacteria in mice, polymixon is a highly effective agent with a favorable ratio of therapeutic to lethal dose.

Aerosporin is bactericidal in action, not bacteriostatic. Time, the number of organisms, and the concentration of aerosporin affect its antibacterial activity. One of the disadvantages of aerosporin therapy may be seen in the observations that the antibiotic is not detectable in effective concentrations in the bile, urine, or cerebrospinal fluid after its parenteral injection The available evidence suggests that aerosporin is of large molecular size and that for this reason it does not pass readily through the kidney barrier.

Parenteral administration is necessary for the production of adequate antibacterial levels in the circulating blood. Injections which are given intramuscularly or subcutaneously produce high antibiotic titers for relatively short periods of time. Maintenance doses are therefore necessary every four hours, the usual dose being 8 mg. per kilogram of body weight. When given orally, aerosporin is not absorbed in significant amounts from the alimentary tract, but it is effective in decreasing greatly the number of intestinal bacteria.

Aerosporin preparations have not exhibited histamine-like reactions when administered subcutaneously to mice or humans. Tenderness and pain occurring at the site of injection have been slight or moderate. In about one-third of the author's cases treated with full therapeutic dosage, some evidence of toxicity such as vertigo, headache, albuminuria, and hematuria occurred.

In the therapy of surgical lesions, we have found it to be less effective in general than streptomycin in the cases studied. In gram-negative bacteremias and mixed infections of wounds, satisfactory responses were obtained.

AUREOMYCIN

One of the most promising of the new chemotherapeutic agents, aureomycin has been found to have considerable antibacterial action *in vitro* against a wide range of gram-positive and gram-negative bacteria, but *Proteus vulgaris* and *Pseudomonas aeruginosa* are relatively resistant Paine, Collins, and Finland determined the sensitivities to aureomycin of 186 strains of bacteria isolated from patients in the Boston City Hospital. This agent apparently possesses antibacterial activity equal to streptomycin against most gram-negative bacilli. It has also been found to be less effective *in vitro* than penicillin but more effective than streptomycin in the case of most coccal organisms. Aureomycin possesses equal antibacterial activity against penicillin-sensitive and penicillin-resistant gram-positive pyogenic cocci as well as against streptomycin-sensitive and streptomycin-resistant bacteria It is also effective against streptomycin-dependent organisms. In addition, there is increasing evidence of its antirickettsial activity and antivirus activity. Most of the bacteria studied did not become resistant readily to aureomycin *in vitro*. Aureomycin hydrochloride, in the form of a crystalline powder, is a stable preparation.

Pharmacologic studies in animals indicate that the toxicity of the drug is low except after intravenous administration when hemoglobinuria and anemia have been noted. In humans therapeutic doses up to 60 mg. per kilogram of body weight per day given orally have not been associated with any toxic manifestations

treatment of human beings, it has been used successfully in experimental staphylococcic infections in rabbits.

Gliotoxin

Gliotoxin is an antibiotic agent which has been obtained from cultures of *Trichoderma lignorum*, *Gliocladium fimbriatum*, *Aspergillus fumigatus*, and other fungi. It appears to be active principally against certain gram-positive bacteria, particularly staphylococci, pneumococci, and streptococci, and much less active against the various gram-negative pathogenic bacteria *in vitro*. It is also highly active against fungi. Its empirical formula, suggested by Johnson, Bruce, and Dutcher, is $C_{14}H_{14}N_2O_4S_2$. As is true of many other antibiotic agents, it is exceedingly toxic for experimental animals, its toxicity approaching that of actinomycin It therefore holds little or no promise as a valuable chemotherapeutic agent. Its therapeutic possibilities in the treatment of fungus infections by topical application might be considered further, however.

Fumigacin (Helvolic Acid) and Fumigatin

Fumigacin, also known as helvolic acid, is an antibiotic agent derived from cultures of *Aspergillus fumigatus*. It has been obtained in a crystalline state and its formula is proposed to be $C_{32}H_{44}O_8$ It is heat-stable, readily inactivated by strong alkalis, and readily soluble in ether, alcohol, chloroform, or acetone. Fumigacin is active against gram-positive organisms *in vitro*, less so against gram-negative bacilli, and least so against fungi. It has a relatively low immediate toxicity for the lower animals after parenteral administration, but unfortunately its prolonged administration in experimental animals produces severe hepatitis In large doses, it has been shown to possess some therapeutic activity in the treatment of experimental streptococcal infections in mice, but has not been employed in the treatment of human beings.

Fumigatin is also produced in the growth of *Aspergillus fumigatus*. It is a colorless quinone with the formula $C_8H_8O_4$. Being feebly bactericidal *in vitro* against gram-positive and gram-negative bacteria, fumigatin is too toxic for consideration as a chemotherapeutic agent in human beings at the present time.

Claviformin, Clavacin, and Patulin

Claviformin is produced by a growth of *Penicillium claviforme* Clavacin is obtained from the *Aspergillus clavatus*, and patulin is derived from *Penicillium patulum*. These substances were described by three different groups of investigators, although it is now generally agreed that all three, though derived from different organisms, are identical The formula has been described as $C_7H_6O_4$. Clavacin is highly bacteriostatic and bactericidal for gram-positive and gram-negative organisms *in vitro*, although its activity is limited by the presence of blood, pus, and serum. It has also been shown to be fungicidal *in vitro* for *Manila albicans* and *Oidium asteroides* In addition, it is described as being capable of inactivating tetanus toxin *in vitro* Patulin underwent some clinical investigation because it was effective against both the gram-positive and gram-negative bacteria commonly present in the nasopharynx. Raistrick and his associates used the substance locally or topically for treatment of patients suffering

It has also been described as a thermostable substance which is lipoid in nature. Wrede and Strack in 1924 found that the *Pseudomonas pyocyanea* produced not only the enzyme, pyocyanase, but also pyocyanine, a blue pigment which is soluble in chloroform and is thermostable. These antibiotic agents were moderately active *in vitro* against a wide variety of gram-positive and gram-negative bacteria, but both were toxic for experimental animals, the intraperitoneal injection of 2 mg of pyocyanine resulting in the death of animals according to Schoental Pyocyanase and pyocyanine have not, therefore, been of any significant value in the management of infections although they have been tried topically for this purpose

ACTINOMYCIN A AND B

These have been derived from *Actinomyces antibioticus*, and possess marked activity against a wide variety of gram-positive bacteria. Actinomycin A is orange colored, soluble in ether and alcohol, thermostable, and highly toxic for experimental animals. Its antibacterial effect is highly bacteriostatic and slowly bactericidal Actinomycin B is colorless, soluble in ether, insoluble in alcohol, and also exceedingly toxic for experimental animals. Its action is also slightly bacteriostatic, but highly bactericidal Doses of 1 mg per kilogram by intravenous injection in mice have produced death by respiratory failure. Efforts to remove the toxic properties and yet preserve the antibacterial activity have thus far been unsuccessful, and therefore neither substance has proved to be of any therapeutic significance.

PENICILLIC ACID

Penicillic acid is a colorless compound derived from both *Penicillium puberulum* and *Penicillium cyclopium* It is readily soluble in water and possesses considerable antibacterial activity against many gram-positive and gram-negative bacteria as well as yeast Penicillic acid has been obtained in crystalline form and has been synthesized. The latest chemical formula proposed is $C_8H_{10}O_4$. Little information has been obtained as to its possible therapeutic value, although it has been recently shown to be toxic on subcutaneous injection in experimental animals

CITRININ

Citrinin is an antibiotic substance whose source is in cultures of *Penicillium citrinum* and *Aspergillus candidus*. It is a yellow compound which has been obtained in crystalline form, its suggested formula being $C_{13}H_{14}O_5$. It is predominantly active against gram-positive bacteria, especially staphylococci and streptococci. On repeated exposure to this substance, bacteria apparently become more sensitive to its action When administered either orally or intraperitoneally, it has been found to be toxic for experimental animals, the toxic symptoms produced include ataxia, respiratory irregularity, convulsions, and a fall in body temperature occurring immediately after its administration After its intravenous injection in rabbits, it may produce depressor effects, and delayed death may occur up to 14 days after injection. At the present time, its toxicity precludes its use as a therapeutic agent. Although it has not been used in the

parenterally, the toxicity is much greater. Although they inhibit the growth of both gram-negative and gram-positive bacteria in extremely high dilutions *in vitro,* they are ineffective *in vivo* in experimental animals. Consequently, they are not used for chemotherapeutic purposes at the present time.

Penicidin

Penicidin is an antibiotic substance derived from various species of Penicillia. It is soluble in ether, alcohol, chloroform, and dilute acids, but is insoluble in petroleum ether. It is active against both gram-positive and gram-negative bacteria including *B typhosus.*

Canavalin

Canavalin is an antibiotic substance identified by Farley from flour made from the soybean or jack bean. It is active against both gram-positive and gram-negative bacteria *in vitro* and is well tolerated by both the lower animals and human beings without ill effects It has been administered intravenously in doses of about 30 cc. per day in the treatment of 13 cases of pneumonia, some of which were complicated by empyema and septicemia with therapeutic effects.

Chlorellin

Chlorellin is an antibiotic substance derived from cultures of the algae *Chlorella vulgaris* and *Chlorella pyrenoidosa.* It was discovered by Pratt and his colleagues and it is active *in vitro* against staphylococci, hemolytic streptococci, *B. subtilis, B. coli,* and *B. pyocyaneus.*

Allicin

Allicin was derived by Cavillito and his associates from Allium sativum (garlic), Allium triquetrum, and Allium cepa Its formula is said to be $C_6H_{10}OS_2$. It has been found to be active *in vitro* against staphylococci, streptococci, *B. subtilis, B typhosus, Vibrio cholerae,* and other bacilli of the colon-typhoid-dysentery group.

Chlorophyll

Chlorophyll is extracted from fresh or dried leaves. Its chemical formula is complex, probably being $C_{55}H_{72}O_5N_4Mg$. By parenteral and oral administration, it is practically nontoxic for the lower animals. Intravenous injections in humans have not produced toxic effects It has been found to manifest some degree of bacteriostatic activity *in vitro* against staphylococci, hemolytic streptococci, *B coli, Pseudomonas pyocyanea, Cl welchii,* and *Cl. histolyticum,* but it is low in bactericidal activity. Its antibacterial activity appears to be due to some interference with the oxygen reduction mechanism of bacterial respiration. It has been used topically in the treatment of various localized infections, particularly burns.

Dicumarol

Dicumarol is derived from spoiled sweet clover hay. In addition to its effect on prothrombin, it exhibits bacteriostatic activity for gram-positive bacteria.

from upper respiratory infections Solutions of 1:10,000 were sprayed into the nose. However, neither claviformin, clavacin, nor patulin is suitable for subcutaneous or intravenous administration since experimental animals died shortly after intraperitoneal injection of each Clavacin is surpassed in toxicity, according to Robinson, only by actinomycin and gliotoxin. It is toxic for leukocytes in amounts smaller than those required for bacteriostasis.

Aspergillic Acid

Aspergillic acid was derived from cultures of *Aspergillus flavus* by White and Hill in 1943 It has been obtained in crystalline form and its formula is considered to be $C_{12}H_{20}N_2O_2$. The compound is thermostable and freely soluble in alcohol, ether, and acetone. Its antibacterial effect is against both gram-positive and gram-negative bacteria, including the Clostridia associated with gas gangrene. It is also effective against the tubercle bacillus *in vitro*. However, the agent is too toxic to be administered systemically Aspergillic acid is highly toxic for the lower animals by parenteral administration. It has not, therefore, been used in the treatment of human beings nor is it likely to be in its present state.

Flavacin

Flavacin was derived from cultures of the Aspergillus flavus by Bush and Goth in 1943 Its chemical nature resembles that of penicillin. It is thought to be 3-pentenyl penicillin.

Flavacidin

Flavacidin is an antibiotic substance derived from cultures of *Aspergillus flavus* by McKee, Rake, and Houck in 1944. Flavacin and flavacidin are entirely unlike aspergillic acid but they appear to be identical substances. Like penicillin, their toxicity in lower animals is extremely low.

Philpot has also described an antibiotic agent derived from cultures of *Aspergillus giganteus* and designated by him as gigantic acid. Its properties, like those of flavacin and flavacidin, are closely similar to those of penicillin. It has not been employed in the treatment of human beings

Penatin

In 1942, Kocholaty found a second antibacterial substance which was produced by cultures of *Penicillium notatum*. He named the substance penatin, which he [illegible] against gram-positive bacteria, [illegible] purified form, it appears [illegible] dilutions than penicillin. Its activity is dependent upon the presence of glucose, which is decomposed by the substance with the production of an unidentified acid and hydrogen peroxide. Coulthard and his associates found a second antibacterial substance and filtrates of *Penicillium notatum*, which they called *notatin*, and shortly thereafter, Roberts and his colleagues isolated an antibacterial substance to which they gave the name, *Penicillin B*. All three of these substances, penatin, notatin, and Penicillin B, have many similar properties which indicate the probability that they are one and the same. When administered orally, the toxicity is low, but when injected

to be effective and their continuation for five to seven days after the general and local manifestations of the infection have been controlled. Relapses, recurrences, and the development of resistant strains of bacteria may occur if this is not done.

(3) It is necessary for the chemotherapeutic agent to reach the infecting bacteria. This requires surgical drainage of localized abscesses and removal of infected slough and sequestra. Bacterial infections of special areas into which the agent is not readily diffused from the blood stream generally require supplemental topical application of the antibiotics. The use of such agents as penicillin topically in the treatment of superficial infections is still disputed. Some investigators, led by Lyons, have indicated their belief that these agents should not be used topically in this manner. Other investigators, including Colebrook, Meleney, Lockwood, and the writer, believe that some of the chemotherapeutic agents, particularly penicillin and bacitracin, may be used effectively in selected cases. The local instillation of antibacterial agents into fresh wounds is not advocated, however.

(4) The infecting bacteria must be sensitive to the antibacterial agent during the entire period of treatment. In general, it is still considered better practice to administer the chemotherapeutic compound in such a manner as to maintain a therapeutic concentration in the blood and tissues at all times. There are notable exceptions to this general rule, however, particularly in the case of penicillin. The development of resistant bacteria by inadequate dosage or unsatisfactory routes of administration can often be avoided. If abscesses are present, they should be drained as soon as feasible.

(5) In general, the chemotherapeutic agents are more effective in controlling established infections than they are in preventing them. Chemotherapy with penicillin or sulfadiazine will not prevent the development of postoperative wound infections. It will, however, prevent the infection from becoming invasive or otherwise attenuate it in the great majority of instances. In the treatment of contaminated wounds, experimental and clinical experience indicates that local chemotherapy is not indicated The prevention of infection in contaminated wounds is primarily dependent upon good surgical treatment. If devitalized tissue or foreign bodies are present within a wound, it is practically impossible to prevent their contamination and infection. If the circulation becomes seriously impaired by thrombosis or tissue destruction, the effectiveness of penicillin therapy is noticeably decreased. No chemotherapeutic agent or any other form of treatment known at present is capable of rendering retained devitalized tissue sterile. Therefore, it is far more practical to do a thorough surgical cleansing or debridement of a wound than to attempt to sterilize devitalized tissue contained within it. In fact, a surgically clean wound requires no chemotherapy except possibly against the accidental invasion of highly virulent bacteria such as the hemolytic streptococcus.

(6) Chemotherapy is more effective in the early stages of an infection, when the lesion is still characterized by diffuse cellulitis and hyperemia. At this time, complete and spontaneous resolution of the infection with little or no breakdown of the tissues by necrotizing toxins of the bacteria or impairment of the blood supply secondary to infectious thrombosis of adjacent vessels may usually be expected The longer chemotherapy is postponed, the greater will be the probability of local suppuration, gangrene, or sequestration.

(7) In general, the chemotherapeutic agents must be considered valuable

In dilutions of 1:50,000 it inhibits *Staphylococcus aureus*, *Staphylococcus albus*, and *Streptococcus pyogenes*. In dilutions of 1:25,000 it inhibits *Pasteurella avicida*.

USTIN

Ustin was derived from cultures of the *Aspergillus ustus* in 1946. It inhibits the growth of gram-positive cocci and Microbacteria, including pathogenic tubercle bacilli, at dilutions of 1:500,000. It has no antibacterial activity against gram-negative bacteria. Its action is inhibited by alkalinity, serum albumin, and other organic substances. Its formula is probably $C_{19}H_{15}O_5CL_3$.

GENERAL PRINCIPLES OF CHEMOTHERAPY

The general principles of practical chemotherapy are now well established and their correct application is necessary for intelligent treatment of surgical infections.

(1) Early and accurate diagnosis is as important as ever for successful management of acute surgical infections. The tendency to treat undiagnosed fevers and ailments with penicillin and other antibacterial agents is haphazard, and the results generally unsatisfactory.

(2) [illegible] of bacteria recovered in bacteriologic cultures. In certain instances it will be impossible to obtain cultures of the etiologic agent, and in others the results of bacteriologic studies will be delayed for one or more days. If infective material is available for smear and gram stain, a presumptive diagnosis of the etiologic agent may be obtained. Likewise, the nature and appearance of a lesion may often suggest the etiologic agent to an experienced surgeon and indicate to him the antibacterial agent which will probably be effective. Treatment may then be started promptly since time is such an important factor in rapidly invasive infections. Meanwhile, aerobic and anaerobic cultures should always be made in serious or severe infections to identify the specific infecting bacteria whenever possible and to determine their susceptibility to the various antibacterial agents. With this method a more accurate selection of the proper agents may be made. However, it must be remembered that bacteriologic cultures, just like any other laboratory procedure, may be influenced by many factors and their results may be delayed, faulty, or misleading. Many patients, when first seen by the surgeon, will already have been given sulfonamides or penicillin, and these substances may be present in the blood and wound exudates in sufficient quantities to make the bacteriologic cultures unreliable. At this time, a positive culture obtained from a lesion may not necessarily indicate the responsible infecting micro-organism. The sulfonamide or antibiotic agent may have suppressed the etiologic agent, eliminating it from the general circulation, but not from hidden secondary foci. Cultures taken in patients who are receiving sulfonamide therapy should contain 1 mg. of para-aminobenzoic acid per 100 cc. of the media used. Likewise, the media should contain penicillinase in a concentration of 10 units per 15 cc. of the culture medium when the patient has been receiving penicillin. A practical antagonist for streptomycin has not been made available.

Adequate chemotherapy implies the administration of sufficiently large doses

tion. When abscess formation occurs, the pus formed is usually thick, crea odorless, and of a yellow or reddish-yellow color. In the majority of instan the responsible staphylococcus is hemolytic, coagulates human plasma, lique fibrin and gelatin, and is sensitive to penicillin. Its ability to coagulate plas is probably the best evidence of pathogenicity.

The successful treatment of a staphylococcal abscess depends upon e diagnosis, and the application of established surgical principles, consisting adequate drainage of the abscess, rest, elevation, and immobilization if feasi If pus or necrotic tissue is present in localized staphylococcal infections, t removal by adequate drainage is extremely important, for once they extruded, healing usually follows promptly. Chemotherapy is recommended an adjunct to penicillin used in average dosage. If the infecting organ is resistant, bacitracin, streptomycin, aureomycin, and chloromycetin are th peutic possibilities and may be used effectively.

Sutured wounds showing signs of abscess formation due to staphyloco infection should first be reopened by removal of the sutures and spreading the edges with a hemostat at the point of maximum pain, swelling, or fluctat The opening is then enlarged adequately to the size of the cavity, irriga gently with saline solution, and loosely packed open with gauze. Careful dress technic minimizes the danger of secondary infection.

STAPHYLOCOCCAL SEPTICEMIA

Penicillin is the antibacterial agent of choice for the treatment of staphyloco septicemia, and its intelligent use has significantly reduced the high morta and prolonged morbidity of this condition (Figs. 3 and 4). At the Cincin General and neighboring hospitals, it has reduced the mortality from appr mately 70 per cent to 30 per cent since 1942. Thus the mortality-recovery r has been reversed by the use of penicillin. The 30 per cent mortality is too high, however, and it could be further reduced by earlier diagnosis treatment before the infection becomes overwhelming or the patient's condit moribund

TABLE IV

RESULT OF PENICILLIN THERAPY IN STAPHYLOCOCCAL SEPTICEMIA TREATED WITH PENICILLIN

	40 Cases Treated with Sulfadiazine, Bacteriophage, etc 1940–1943 (Per Cent)	*76 Cases Treated with Penicillin* 1943–1949 (Per Cent)
Mortality	67 6 (27 deaths)	31.5 (23 deaths)
Recovery	32 5	68 5

In the past, the circulating bacteria were filtered out of the blood by reticulo-endothelial system, and often produced secondary or tertiary metast in the viscera even when surgical attack removed or seemed to control primary distributing focus. Because the metastatic abscesses were freque multiple and often inaccessible to surgery, the patient surviving the prim initial infection frequently succumbed to the later infectious complications. these reasons and because of the lack of a method to control the staphylococ

adjuvants to correct surgical procedure, but not substitutes for it. The ultimate control of an infection by prolonged and protracted chemotherapy is not justifiable merely to pursue a completely nonsurgical program of management

(8) A lag of 24 to 72 hours may occur before a chemotherapeutic response is obvious. The duration of this lag period for hemolytic streptococcal infections may be 12 to 24 hours whereas it may be as long as 48 to 72 hours in hemolytic staphylococcal lesions (Fig. 11). If evidence of the clinical response to the general and local manifestations of an invasive susceptible infection does not occur within 72 hours, a careful search should be made for associated diseases or metastatic complicating infections.

(9) In mixed infections, combined chemotherapy of penicillin with sulfadiazine, streptomycin, chloromycetin is indicated.

(10) The topical route of administration for chemotherapeutic agents is most conducive to establishing a state of sensitization in the patient. Therefore, these agents should not be used locally unless they are definitely indicated. In general, the incidence of toxic reactions increases with the duration of chemotherapy. The thoughtless or unnecessary topical or systemic administration of chemotherapeutic agents may lead to sensitization of a patient which will deprive him of the future use of a valuable, perhaps life-saving antibacterial agent.

(11) The early recognition and proper evaluation of toxic manifestations of chemotherapy are necessary for the intelligent use of these agents and for the safety of the patient To do this, it is necessary to examine and question the patient daily Complaints of headache, generalized aching, and a feeling of malaise should be noted and evaluated The skin and mucous membranes of the mouth should be examined daily for signs of a rash, jaundice, or pallor. Any complaint of a sore throat after the initiation of therapy except in upper respiratory tract infections should be viewed with immediate suspicion, since it may be the first sign of agranulocytosis. The urine should be examined frequently and an intake-output chart on patients receiving chemotherapy should be maintained. If the urine output is decreasing in spite of adequate intake, it is likely that a renal complication is developing. Laboratory examinations of the blood, including blood level assays, should be done at frequent intervals as described earlier In patients receiving streptomycin, a daily examination with the audiometer should be made for acuity of hearing and for signs and symptoms of vertigo by the caloric test

(12) Concomitant general supportive therapy is important to restore altered physiologic states to normal or near normal. Physiologic derangements that may be associated with severe infections include dehydration, anemia, hypoproteinemia, and decreased blood volume This is particularly true in the chronically ill patient whose resistance has been depleted by continued infections.

CHEMOTHERAPY OF SELECTED SURGICAL INFECTIONS

Staphylococcal Abscesses

As a rule, staphylococcal infections tend to be localized, producing an area of cellulitis which subsequently undergoes central necrosis and abscess forma-

(6) Cavernous sinus thrombosis

(7) Pylephlebitis

Although penicillin therapy should be started as soon as the diagnosis is made, it is important to determine at once the relative susceptibility of the infecting

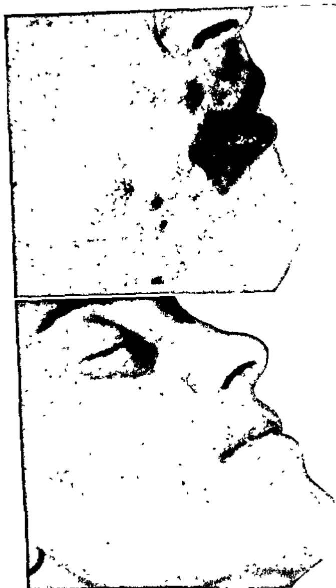


FIG 4 –(A) V L, 28-year-old white female with carbuncle of face, hemolytic *Staphylococcus aureus* septicemia, bilateral staphylococcal pneumonia, and septic thrombophlebitis of external jugular vein Temperature 103° F Parenteral penicillin therapy started (B) Same patient's appearance 10 days later All evidence of infection has been controlled.

organism to penicillin as well as other available agents, including streptomycin, bacitracin, aureomycin, and chloromycetin. If the organism is resistant to penicillin, any of these other agents may be used successfully.

The dose of penicillin recommended for this condition is 25,000 to 100,000 units of crystalline penicillin G administered by the intramuscular route at intervals of three hours, day and night, until the infection has been brought under control.

in remote or unrecognized areas, the mortality in established staphylococcal septicemia was high, varying between 60 and 90 per cent in different series. When the infection spread to the meninges or became engrafted upon heart valves, the mortality approached 100 per cent

Experience has shown treatment to be most successful in young adults or children in whom the diagnosis of staphylococcal bacteremia was made early, penicillin given promptly and intensively, and surgical drainage could be done when indicated Treatment which was not prolonged until the blood cultures

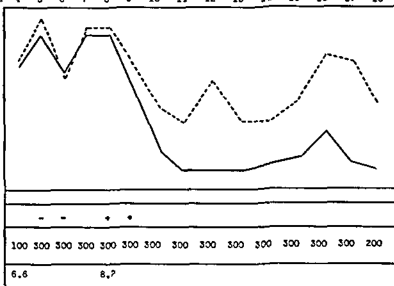


FIG 3 —R N, 16-month-old colored male admitted on March 21, 1948 with hemolytic *Staphylococcus aureus* septicemia Response to penicillin therapy with prolonged interval dosage schedule of 100,000 units every eight hours was satisfactory with control of the infection, clearing of the blood stream, and recovery of the patient The time lag, however, was longer than usual

became negative and the temperature normal for at least seven days, predisposed to relapse The outcome in the individual case was dependent upon many factors, including the age of the patient, the susceptibility of the strain of staphylococcus to penicillin, the site and nature of the primary infection, the duration of the bacteremia, the presence and location of secondary or metastatic abscesses, the accessibility of the primary or secondary infections to surgical drainage, and the presence of other associated and complicating diseases. A review of the fatal cases of staphylococcal septicemia treated unsuccessfully with penicillin revealed the following responsible factors or complications

(1) Acute vegetative endocarditis
(2) Infected burns of 60 per cent or more of the body surface
(3) Pemphigus
(4) Intraventricular rupture of an unrecognized brain abscess.
(5) Penicillin-resistant strain of infecting organism





A B

Fig. 5.—E.H., 43-year-old white female with diabetes who was admitted to the Cincinnati General Hospital on August 2, 1944 with a large carbuncle on the neck of 10 days' duration. (A) Appearance of the carbuncle on August 3, 1944 at the start of penicillin therapy. (B) Disappearance of the carbuncle and almost complete healing have occurred in nine days. Temperature and pulse remained normal after the third day.





A B

Fig 6.—W H., 52-year-old white diabetic male with carbuncle of neck of 14 days' duration. Only partial resolution occurred under treatment with penicillin and incisions were used to remove necrotic slough and drain purulent material. (A) The appearance of the carbuncle at the start of parenteral penicillin therapy. (B) Necrotic material in center of carbuncle has been removed surgically and healing by granulation is progressing satisfactorily.

Thereafter the individual dose may be progressively decreased. The injection of 300,000 units of procaine penicillin alone or in combination with 100,000 units of aqueous penicillin intramuscularly may be used satisfactorily every 12 hours in staphylococcal septicemia After the infection is brought under control, the dose may be administered once daily. Oral penicillin is not recommended for this condition

Carbuncles

A carbuncle is essentially a spreading and necrotizing staphylococcal infection of the deeper layers of the skin and subcutaneous tissue which may result in extensive necrosis, sloughing, liquefaction of the subcutaneous tissue, septicemia, and death The many forms of treatment which have been devised for carbuncles are an indication of our inability to control the locally or generally invasive characteristics of this infection in the past. The majority of surgeons have

TABLE V

Result of Penicillin Therapy in One Hundred Consecutive Cases of Carbuncle

Clinical Result	*Surgery*	*No Cases or Percentage*
Spontaneous resolution	None	41
Partial resolution with necrosis	Incision	26
Abscess formation	Incision	28
Failure	Excision	4
Deaths	None	1

learned to employ crucial incisions or excision, and because of the tendency of carbuncles to extend locally or invade the general circulation, the treatment of choice at many clinics, including the Cincinnati General Hospital, has been radical excision.

Sulfonamide therapy has been disappointing because of natural resistance of the hemolytic *Staphylococcus aureus* Penicillin has revolutionized the management of this condition and it is obviously the chemotherapeutic agent of choice. When given early in sufficient dosage, it has brought the general and local invasive manifestations under control within a period of 48 to 72 hours, and so modified the subsequent course that both mortality and morbidity were significantly reduced Complete and spontaneous resolution occurred in 41 0 per cent of the cases (Fig 5), partial resolution with centralized necrosis in 26 0 per cent (Fig. 6), partial resolution and abscess formation in 28 0 per cent, and failure in 4 per cent Since the invasive qualities of this lesion have been controlled effectively with penicillin, radical excision of carbuncles is rarely necessary Instead, limited surgical procedures are recommended when indicated, consisting of incision and drainage of abscesses which occur during the therapy and excision of necrotic tissue When the infecting bacteria are resistant to penicillin, streptomycin, bacitracin, aureomycin, or chloromycetin may be effective For the treatment of carbuncles, crystalline penicillin G may be administered in aqueous solution in doses of 15,000 to 25,000 units every three hours The repository form of penicillin may likewise be administered in dosage of 300,000



FIG 7.—J H., white, age 11, illustrating the definite control of an early case of acute hematogenous osteomyelitis of the tibia by prompt and adequate penicillin treatment. Serial roentgenograms reveal complete healing with minimal residual damage and without sequestration, osteosclerosis, joint limitation, or abnormality of growth. (A) (11/13/44) No evidence of bone involvement at the start of penicillin therapy. (B) (12/16/44) The extent of bone involvement by the infection is indicated by periosteal reaction of the lower end of the tibia and localized rarefaction in shaft of tibia about 5 cm. above the epiphysis. (C) (2/23/45) Healing of the involved area has started with beginning recalcification of the previously described area of demineralization. (D) (7/16/45) Recalcification is complete. There is no evidence of active infection. (E) (5/16/47) No evidence of active infection, sequestration, or sclerosis has developed. A normal roentgenographic appearance of the bone has been re-established.

or 400,000 units every 24 to 48 hours successfully. Preparations containing 300,000 units of procaine penicillin and 100,000 units of aqueous penicillin have been satisfactory A dosage of 100,000 to 200,000 units every eight to 12 hours in aqueous solution administered intramuscularly has also proved to be effective in this condition.

ACUTE HEMATOGENOUS OSTEOMYELITIS

Penicillin is a powerful and effective chemotherapeutic agent in the management of acute osteomyelitis, and it has greatly modified both the management and roentgenographic interpretation of this disease In our experience, it has reduced the mortality to 1.4 per cent in all cases seen in hospital and surgical practice.

In the past, the results of treatment in this condition have been unsatisfactory for several reasons. Difficulties in diagnosis often resulted in delay and spread of the process with extensive destruction of the bone. When early diagnosis was made, the principal method of arrest and control of the necrotizing process was emergency decompression of the involved area by surgical drainage followed by prolonged periods of immobilization More recently, chemotherapy with the sulfonamides as a supplement to surgical intervention has aided in the control of the infection, but has left much to be desired Penicillin, on the other hand, has had a profound effect on acute hematogenous osteomyelitis and has greatly

In general, the results of penicillin therapy have varied primarily with the time of diagnosis and the start of treatment (Figs 7-10). The earlier the onset of therapy the more brilliant the result, while delays were associated with more extensive destruction of bone, more frequent formation of abscesses, and sequestration If there is any doubt as to the presence of an acute osteomyelitis, it is better to start penicillin therapy immediately rather than wait until the diagnosis is proved A dose of at least 20,000 units of penicillin should be given intramuscularly or intravenously, and repeated every two or three hours for at least seven days after the signs of infection are well under control, a period of three or more weeks usually being required. In severe infections, doses of 50,000 to 100,000 units may be given at the same interval until a clinical response has been obtained Obviously, it is not indicated in acute hematogenous osteomyelitis caused by gram-negative or other penicillin-resistant bacteria

The effects of penicillin include control of the generalized infection with sterilization of the blood stream, reduction of the mortality rate, and decrease in the incidence of metastatic or secondary infectious complications (Fig. 11) If metastatic complications such as staphylococcal pneumonia, pleuritis, pericarditis, or thrombophlebitis already exist, penicillin is a powerful chemotherapeutic agent in their control as an adjunct either to surgical or conservative treatment. There seems to be little doubt that early and adequate penicillin therapy has made surgery for emergency decompression of the infected bone unnecessary in the majority of instances, especially during a period when the patient is often desperately ill with a generalized infection. Instead, control



FIG. 9—R J, a three-year-old Negro boy with acute hematogenous osteomyelitis of the radius which was undiagnosed and untreated with penicillin until 23 days after the onset of the disease. Penicillin therapy failed to control the infection completely, which produced subsequent sequestration, multiple abscesses, and recurrent exacerbations. (A) (6/20/44) Rarefaction at distal end of radius, most likely early osteomyelitis. (B) (6/29/44) Rarefaction has extended upward through distal half of radius and also involves the proximal one-fourth; several breaks in the cortex, periosteal reaction present, especially proximal end. (C) (7/8/44) Increased periosteal reaction with extensive demineralization of both ends of the radius. (D) (7/15/44) Very extensive periosteal reaction with absorption of both ends of the shaft and beginning sequestration of the middle third. (E) (10/27/44) The sequestrum representing the middle third of the radial shaft has been partially absorbed and apparently partially revitalized; healing is progressing. (F) (7/5/46) Further reconstruction of the radius; small sequestrum remains within an area of decreased density near the junction of the upper and middle thirds.

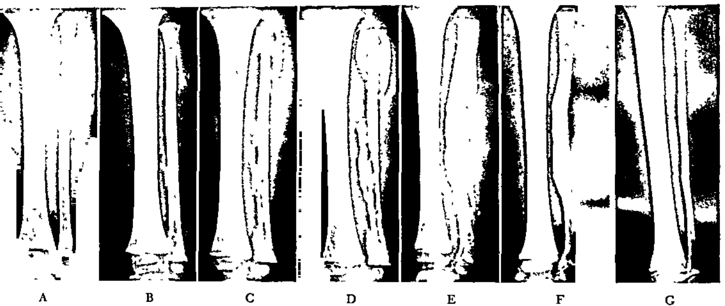


Fig 8 —J C, a 13-month-old white male infant, was admitted to the Cincinnati Children's Hospital on October 23, 1943 with acute hematogenous osteomyelitis of the left fibula of four days' duration. Relapse of infection occurred promptly after cessation of treatment with an inadequate dosage of penicillin over a nine day period. Sequestration occurred, but the final result after further and adequate penicillin therapy was good The roentgenographic changes occurring in this infection are examples of the effectiveness of penicillin and the remarkable healing power of bone (A) (10/23/43) No definite x-ray findings in bone or periosteum, marked soft tissue swelling (B) (11/4/43) Rarefaction at proximal and distal ends of fibula with associated periosteal reaction, also an area of periosteal reaction at level of junction of middle and lower thirds. (C) (11/25/43) Bone destruction involving lower two-thirds of fibula, absorption of proximal end, marked periosteal reaction in these areas, practically two-thirds of shaft is sequestrating. (D) (1/18/44) Marked periosteal reaction along the entire shaft of fibula, the sequestrum has been partially absorbed. (E) (4/24/44) Fibular shaft is being reformed by new bone associated with the periosteal reaction; a long thin sequestrum which has undergone further absorption remains on the outer portion of the fibula in its middle third. (F) (9/8/44) Sequestrum has been previously removed, healing process has produced reconstruction of fibula with moderate irregularity and sclerosis of its middle third. (G) (6/5/47) Healing process apparently complete with straightening of fibula and marked decrease in sclerosis of this bone; moderate thickening of cortex remains, growth of bone has been normal.

of the infection by penicillin has also permitted correction of the altered physiology and adequate treatment of the metastatic complications. When abscesses developed, surgical drainage was done more safely and more effectively at a time when the patient was in a better condition, under the protective screen of parenterally administered penicillin. In addition, the cosmetic effects in the cases treated with penicillin were in sharp contrast to those in cases treated by other methods. The long-term curative effects of penicillin in acute hematogenous osteomyelitis are still undetermined. However, recurrences have developed in 9 of 92 cases which we have studied, usually when treatment was late, inadequate, or not sustained. In some instances of severe or fulminating infections, in which the patient would not live 48 or more hours to permit the maximum effect of penicillin, emergency surgical intervention after adequate preoperative preparations is necessary.

Chronic Osteomyelitis

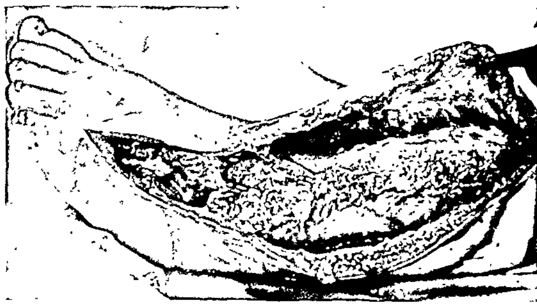
Chronic pyogenic osteomyelitis is a prolonged and disabling disease usually characterized by suppuration with abscess formation, draining sinuses, progressive necrosis of bone, regeneration of greatly thickened and sclerotic new bone, and a diminished capacity for work. The division between acute and chronic osteomyelitis is indistinct, varying with the interpretation of the individual surgeon, and acute exacerbations may occur at any time during the course of this chronic infection. In the past, the lesion has usually required long periods of treatment, hindered the physical development and education of children, produced enforced periods of incapacitation in adults, and resulted in great economic loss

At the present time the management of chronic pyogenic osteomyelitis continues to be a difficult problem. The results of chemotherapy are usually disappointing. In general, treatment may be conservative or operative with chemotherapy as a useful adjunct of variable effectiveness The type of therapy chosen in the individual case should depend upon certain preliminary determinations such as a clinical study of the local lesion, an evaluation of the patient's general condition, roentgen examinations, careful aerobic and anaerobic cultures of the infecting bacteria, and a measurement of the susceptibility of the bacteria to the various chemotherapeutic agents.

For chemotherapy, penicillin and sulfadiazine, administered systemically, are usually recommended In the author's experience, streptomycin has been of questionable or no value because of the rapidity with which the infecting bacteria develop resistance The use of penicillin and sulfadiazine may result in spontaneous resolution of an acute exacerbation, but in the majority of cases, surgical removal of the devitalized and infected bone is most important. When intensive chemotherapy is used for four to seven days preceding radical surgery and for two or more weeks postoperatively, it may aid in the control of infection and may facilitate healing

Acute Secondary Parotitis

Acute secondary parotitis or surgical mumps is an uncommon but serious pyogenic infection of the salivary glands. Its incidence varies between .04 and



preoperative and postoperative penicillin therapy controlled the infection.



Fig 11 –L W , a 12-year-old white male with *Staphylococcus aureus* septicemia and acute hematogenous osteomyelitis of the left humerus treated successfully with parenteral penicillin Note the lag of 72 hours before definite chemotherapeutic response become obvious Blood culture remained positive during this period The definite control of the infection is indicated by sterilization of the blood stream, progressive fall of the elevated temperature, return of white blood count to normal level, and absence of metastatic complications

Recently chemotherapy has had a profound effect on the management of this infection. It controls the infection so well that emergency surgical incision and decompression of the capsule are no longer necessary except in rare instances (Fig. 13). The chemotherapy recommended is the systemic administration of Lugol's solution and penicillin. The general plan of Lugol's solution therapy consists of the administration of 120 to 250 minims per day at the earliest opportunity until definite improvement occurs. Thereafter, as further improvement becomes evident, the daily dose may be progressively reduced. The greater part

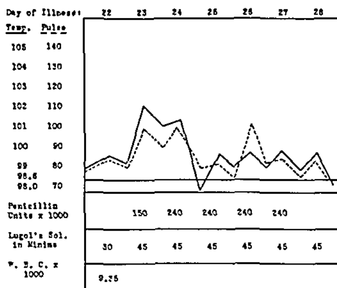


FIG. 13 —M S Case of acute postoperative parotitis in a white female aged 37 years Definite control of the infection followed by spontaneous resolution occurred after therapy with penicillin and Lugol's solution.

is given by mouth whenever possible, and smaller supplemental amounts should be given by hypodermoclysis, intravenous infusion, or proctoclysis. A commonly used schedule consists of the daily administration of 20 minims every three hours by mouth and 60 minims by hypodermoclysis along with 1500 cc. of physiologic saline given to help correct the dehydration. When definite improvement occurs, the intramuscular dose was discontinued and the oral dose was decreased to 15 and later 10 minims every three hours until the process has completely subsided. Penicillin should be given in average dosage, using either 15,000 to 25,000 units of sodium penicillin every three hours intramuscularly, the daily dose of 300,000 units in one of the repository forms of penicillin, or the injection of 100,000 to 200,000 units of aqueous penicillin intramuscularly every eight to 12 hours.

The general response of this infection to both Lugol's solution and penicillin therapy has followed the same general pattern seen in other surgical infections treated by chemotherapy An interval of 24 to 48 hours follows the start of treatment before obvious signs of clinical improvement occur. Thereafter, the improvement is usually progressive and rapid.

In a series of 75 cases of postoperative surgical parotitis, treated at the Cincinnati General Hospital, spontaneous and complete resolution occurred in

.74 per cent of all patients undergoing major surgical operations, the average being approximately 0.5 per cent in collected series. It is important because of its high mortality of 40 to 60 per cent and its tendency to occur in patients debilitated by prolonged illness, severe infections, serious metabolic disturbances, major operations, or extensive injuries. One of the most obvious factors which precipitates this infection is poor oral hygiene; that is, dehydration, mouth-breathing, suppression of salivary secretion, and dental caries favor the development of an ascending infection along Stensen's duct (Fig. 12).



FIG 12 —Acute secondary right parotitis of three days' duration Note the poor hygienic condition of the mouth

The lesion is caused by the pyogenic gram-positive cocci in at least 90 to 95 per cent of the cases The infection has been monomicrobic in our experience in approximately 60 per cent of the cases and polymicrobic in the remainder The hemolytic *Staphylococcus aureus* is the principal infecting agent in two-thirds to three-fourths of the lesions. Nonhemolytic staphylococcus, hemolytic streptococcus, nonhemolytic streptococcus, and *Streptococcus viridans* are of lesser incidence and importance. Gram-negative aerobic bacilli are occasionally associated with the gram-positive pyogenic cocci in this infection

Previously, the surgical treatment of this condition consisted of either incision and drainage of localized abscesses and areas of necrosis after they had developed, or early decompression of the gland by incisions in an attempt to minimize or prevent the development of necrosis caused by increasing pressure within the dense fascial compartments.

Recently chemotherapy has had a profound effect on the management of this infection. It controls the infection so well that emergency surgical incision and decompression of the capsule are no longer necessary except in rare instances (Fig. 13). The chemotherapy recommended is the systemic administration of Lugol's solution and penicillin. The general plan of Lugol's solution therapy consists of the administration of 120 to 250 minims per day at the earliest opportunity until definite improvement occurs. Thereafter, as further improvement *becomes evident, the daily dose may be progressively reduced. The greater part*

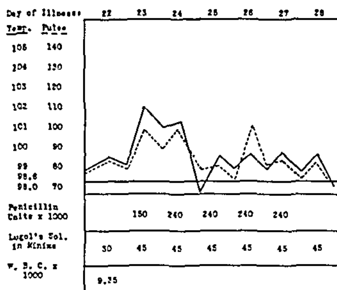


FIG. 13 —M.S Case of acute postoperative parotitis in a white female aged 37 years Definite control of the infection followed by spontaneous resolution occurred after therapy with penicillin and Lugol's solution.

is given by mouth whenever possible, and smaller supplemental amounts should be given by hypodermoclysis, intravenous infusion, or proctoclysis. A commonly used schedule consists of the daily administration of 20 minims every three hours by mouth and 60 minims by hypodermoclysis along with 1500 cc. of physiologic saline given to help correct the dehydration When definite improvement occurs, the intramuscular dose was discontinued and the oral dose was decreased to 15 and later 10 minims every three hours until the process has completely subsided. Penicillin should be given in average dosage, using either 15,000 to 25,000 units of sodium penicillin every three hours intramuscularly, the daily dose of 300,000 units in one of the repository forms of penicillin, or the injection of 100,000 to 200,000 units of aqueous penicillin intramuscularly every eight to 12 hours.

The general response of this infection to both Lugol's solution and penicillin therapy has followed the same general pattern seen in other surgical infections treated by chemotherapy. An interval of 24 to 48 hours follows the start of treatment before obvious signs of clinical improvement occur. Thereafter, the improvement is usually progressive and rapid.

In a series of 75 cases of postoperative surgical parotitis, treated at the Cincinnati General Hospital, spontaneous and complete resolution occurred in

46, partial resolution without abscess formation in 13, partial resolution with abscess formation in 12, and failure in 4 (Table VI).

TABLE VI

RESULT OF TREATMENT OF ACUTE SECONDARY PAROTITIS WITH LUGOL'S SOLUTION AND PENICILLIN

Results	*No. of Cases*
Complete spontaneous resolution	46
Partial resolution without abscess formation	13
Partial resolution with abscess formation	12
Failure	4
Total	75

Although these two chemotherapeutic agents have controlled the invasive qualities of this infection, surgical incision and drainage of abscesses should be carried out as soon as their presence is recognized The successful management of acute secondary parotitis by chemotherapy depends on early diagnosis, adequate and continuous chemotherapy, and intimate contact of the chemotherapeutic agent with the bacteria In addition, general supportive therapy and the indicated treatment for the primary diseases are of obvious importance.

STREPTOCOCCAL INFECTIONS

The majority of streptococcal infections are produced by the aerobic hemolytic streptococcus and these tend to be invasive and to run a rather short course. The local process is usually one of cellulitis with lymphangitis, lymphadenitis, and little tendency to form abscesses (Fig 14). When local breakdown of tissue



A B

FIG 14 —Extensive hemolytic streptococcal cellulitis with cutaneous gangrene and septicemia which was treated successfully with penicillin (A) The nature of the lesion at the start of penicillin treatment is illustrated (B) The clean granulating wound remaining after the infection had been controlled and the necrotic tissue carefully trimmed away by sharp dissection

does occur, it is characterized either by gangrene of the overlying skin or the development of thin, watery pus. Invasion of the blood stream by bacteria from this primary focus is frequent, particularly when ill-advised operative interven-

tion is made upon a streptococcal cellulitis which is locally invasive (Fig. 15). Trauma incident to surgical intervention may cause septic thrombi to break off into the neighboring vessels and the general circulation. The diagnosis is suggested by the presence of a locally invasive infection associated with chills, fever, *rapid pulse, sweats, prostration,* and other signs of toxemia. It is proved by demonstrating the continued presence of bacteria in the blood by careful blood cultures.

Occasionally surgical scarlet fever or erysipelas may result from infection of a postoperative wound, and the hemolytic streptococcus is always associated with *these infections.*

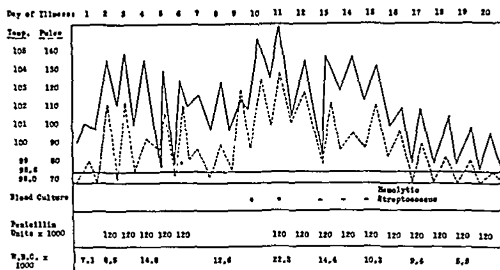


Fig. 15 —Infected compound comminuted fracture of the right tibia and fibula. Inadequate

The treatment of hemolytic streptococcal infections consists primarily in the control of their invasive characteristics by chemotherapy, rest, and hot fomentations, and secondarily in the adequate incision and drainage of collections of pus and necrotic tissue Incisions or manipulations should never be made in streptococcal infections until the invasive characteristics have been overcome, *with the exception of acute hemolytic streptococcal gangrene.* The treatment of the latter condition will be discussed separately. Infections caused by the hemolytic streptococcus respond to chemotherapy with either penicillin, sulfadiazine, or bacitracin, although penicillin is usually the agent of choice for hospitalized patients

In cases of streptococcal septicemia, it is *important to diagnose* the condition early and correctly in order to start specific treatment as soon as possible to minimize the distribution of virulent bacteria to distant areas, and to prevent the formation of secondary metastatic abscesses (Fig. 16). If a suppurative thrombophlebitis is present in the neighboring veins, associated dicumarol therapy or proximal venous ligation or excision should be *considered.*

After control of the invasive characteristics of the infection under the protection of a bacteriostatic concentration of one or more of the chemotherapeutic

agents in the blood, drainage of the local lesion may be instituted when pus or necrotic tissue has been formed General supportive therapy consisting of the administration of adequate fluid and electrolytes and small daily blood transfusions is of definite value. Frequent examinations should be made to detect metastatic infectious complications as early as possible, each of which is treated according to its individual location and characteristics.

Hemolytic Streptococcal Gangrene

Gangrene caused by the hemolytic streptococcus occasionally follows some relatively minor operative procedure or injury The lesion is essentially an

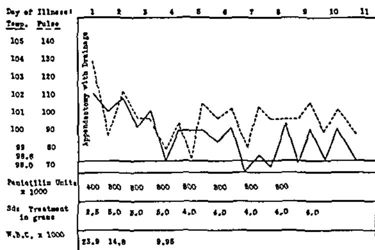


Fig. 16 —L.R , a young adult female with acute perforated appendicitis and generalized peritonitis of 4 5 days' duration The clinical course after appendectomy and combined penicillin and sulfadiazine therapy is illustrated

epifascial, spreading, subcutaneous gangrene with thrombosis of the nutrient vessels and resultant slough of the overlying skin. It usually develops in the extremities, although the perineum, face, and other parts of the body may be involved. It is characterized by the onset of pain and marked swelling at the site of the wound, chills, elevation of the *temperature to 101° to 104° F., rapid* pulse, toxemia, marked prostration, and a rapidly spreading, painful cellulitis which undergoes bullous formation and a peculiar patchy and extending necrosis Hemolytic streptococci are found in the subcutaneous gangrene and bullae, often in pure culture.

Early recognition is imperative for good treatment. Longitudinal *incisions* should be made as soon as possible through and beyond the gangrenous area, contrary to the usual treatment for streptococcal cellulitis This is important if the process is to be arrested. After operation the wound is treated by rest, elevation, continuous compresses with Dakin's solution, and removal of slough by sharp dissection without bleeding during subsequent dressings. Before and after operation, penicillin, sulfadiazine, or bacitracin should be given in adequate amounts An initial dose of 4 gm. of sulfadiazine and 1 gm every four hours thereafter gives a satisfactory result A preoperative dose of 25,000 units of penicillin given intramuscularly followed by 15,000 to 20,000 units every

three hours has proved effective. Daily injections of 300,000 to 400,000 units of one of the repository preparations can be used satisfactorily.

ANAEROBIC STREPTOCOCCAL INFECTIONS

The anaerobic streptococcus may produce severe infections with or without bacteremia, particularly after operative procedures upon the genital, intestinal, or respiratory tracts. The anaerobic streptococcus is one of the most frequent causes of septic abortions and puerperal sepsis. Postoperative peritonitis caused by the anaerobic streptococcus may occasionally complicate operative procedures upon the female genital tract such as removal or drainage of chronic active tubo-ovarian abscesses. This type of peritonitis usually becomes manifest six to eight days after the operative procedure and the general signs of infection may be associated with little or no evidence of intraperitoneal infection until the process is well advanced. Such conditions may be associated with anaerobic streptococcal infections of the wound and occasionally with metastatic abscess formation in distant regions such as the brain.

Infections produced by the anaerobic streptococcus are usually susceptible to penicillin or bacitracin but not to the sulfonamides or streptomycin. Accordingly, in addition to the usual methods of treating infected wounds already described, early and adequate therapy with penicillin or bacitracin is indicated. The management of postoperative peritonitis caused by the anaerobic streptococcus is difficult and the diagnosis may be uncertain. Treatment consists principally of general supportive measures and chemotherapy with penicillin. In general, the dose of penicillin recommended for anaerobic streptococcal infections is relatively high, consisting of 50,000 to 100,000 units every three hours by the intramuscular route If the organism is shown to be highly susceptible, smaller doses may be employed.

EMPYEMA

Empyema most frequently occurs as a complication of pneumonia with infection due to such penicillin-susceptible organisms as pneumococci, streptococci, or staphylococci Otherwise, it may follow penetrating wounds of the chest or rupture of the lung, emphysematous bullae, or pulmonary abscesses. It may also occur after lobectomy, pneumonectomy, or other thoracic operations. Under the latter circumstances, mixed infections may occur with a variety of etiologic agents, including micro-aerophilic and anaerobic streptococci, *Clostridium welchii*, *B melaninogenicum*, *B coli*, *B. pyocyaneus*, etc.

Treatment with penicillin or the sulfonamides of pneumococcal, staphylococcal, and streptococcal pneumonia has greatly reduced the incidence of postpneumonic empyemas, and it has also been effective in the prevention of empyemas following trauma, lobectomy, pneumonectomy, and other thoracic surgical procedures. The treatment of established empyema is primarily surgical Once the pleural exudate has become frankly purulent, closed surgical drainage is indicated, in conjunction with parenteral and intrapleural penicillin therapy or the administration of sulfadiazine. Under this management, the infection is quickly brought under control and early healing is made possible While it is true that recovery, particularly in children, may occur in early acute empyemas with simple aspira-

tions of the exudate followed by sulfonamide or penicillin therapy, this method of treatment is not recommended and it may be dangerous. The earlier the closed thoracotomy is done, the less danger there will be for fibrotic rigid walls to develop about the empyema cavity, preventing subsequent and early re-expansion of the lung after the infection has been controlled. In case of well established empyemas, open thoracotomy with rib resection is preferable.

Acute Septic Peritonitis

Since the majority of cases of acute septic peritonitis is secondary to lesions of the alimentary tract, the treatment is still essentially surgical. During the past 10 years, the mortality of acute septic peritonitis has been progressively diminished, and part of the reduction undoubtedly has been due to the introduction and general use of effective antibacterial agents. The mortality of primary or idiopathic peritonitis caused by the pneumococcus or beta hemolytic streptococcus has been reduced from approximately 80 per cent to 30 per cent or less by surgical drainage and adequate chemotherapy with sulfadiazine and penicillin

Significant decreases in the mortality of secondary peritonitis have also been noted. Our clinical experience during the past six years in 598 cases of acute septic peritonitis secondary to acute appendicitis, perforated peptic ulcers, and penetrating wounds of the abdomen indicates that successful management depends primarily upon early diagnosis and good surgery, and secondarily upon chemotherapy and adequate supportive treatment There is no specific therapy for this infection as yet, and chemotherapy is not a substitute for prompt diagnosis and early operative repair or removal of the primary source of infection before abdominal distention, intestinal stasis, and cardiovascular depression have occurred

A comparison of the results obtained in 685 similar cases treated without chemotherapy reveals that the mortality has recently been reduced approximately 60 per cent The evidence suggests that this reduction is largely due to the effects of chemotherapy.

TABLE VII

Type of Peritonitis	*Cases Treated without Chemotherapy*	*Mortality (per cent)*	*Cases Treated with Chemotherapy*	*Mortality (per cent)*
Appendiceal peritonitis or abscess	338	14 6	244	4 9
Perforated peptic ulcer	143	26 6	160	9 3
Penetrating wounds of abdomen	104	27 9	161	11 5

A comparison of the mortality of three types of peritonitis before and after adoption of chemotherapy.

On the basis of our clinical experience, the chemotherapy recommended for effective treatment of acute secondary peritonitis consists of either the parenteral administration of sulfadiazine and penicillin, the combined use of sulfadiazine, penicillin, and streptomycin, or the injection of large doses of penicillin (Fig 16). When used in combination, the dose of each agent should be therapeutically effective The dosage of penicillin when used singly is a minimum of 100,000 units given at intervals of two or three hours In severe infections, it is our practice to revise this dose upward, giving as high as 500,000 or more units at the same interval. The concomitant use of the three agents, penicillin,

sulfadiazine, and streptomycin, produces a synergistic effect and a significant delay in the development of bacterial resistance. Intraperitoneal instillations of any of the agents are not advocated. The use of streptomycin alone is not recommended. It will be interesting to observe the effectiveness of aureomycin and chloromycetin in this disease.

Earlier it was believed that penicillin would be of little or no value in the prevention or treatment of secondary peritonitis because a large proportion of the infecting bacteria was of the gram-negative variety which was either naturally resistant to the action of penicillin or was a producer of penicillin-destructive enzymes. The experience of Crile, Brown, Pulaski, Blam, and Silvani, as well as our own, however, has shown that these theoretical objections are not valid, and that in reality penicillin in large doses is effective.

A review of our previous experimental work in peritonitis suggests the explanations for penicillin's effectiveness. The bacterial flora of peritoneal exudates was found to be mixed and varied, three or more species of bacteria being recovered from 96 to 100 cases studied, and as many as seven types being occasionally isolated. The organisms recovered consisted of aerobic and anaerobic gram-positive and gram-negative varieties. Other studies indicated to us that the pathogenicity of the bacteria in pure and mixed culture revealed that the majority of the strains tested, particularly those of the gram-negative aerobic bacilli, possessed little or no invasive qualities. When injected subcutaneously they produced only minor local lesions, and they failed to cause a fatal peritonitis when injected intraperitoneally. The majority of the anaerobic bacteria behaved similarly However, if several or more types of bacteria were mixed and injected intraperitoneally, their synergistic effect produced an overwhelmingly fatal peritonitis. On the basis of these results, we concluded that (1) secondary peritonitis is essentially a synergistic infection produced by the accumulative action of the various bacteria, (2) nonpathogenic bacteria may enhance the virulence of other micro-organisms, and (3) the importance of *B. coli* and other gram-negative bacilli in peritonitis is greatly exaggerated, the frequent reference of peritonitis to the unaided activity of *B. coli* being without sufficient justification.

Many of the gram-positive bacteria, both aerobic and anaerobic, are susceptible to the action of penicillin Large doses of penicillin produce sufficient concentration of penicillin to inhibit the growth of these susceptible organisms, thereby reducing the number and varieties of bacteria actively growing in the peritoneal exudate. In this manner the infection is converted from a severe, mixed, and synergistic one to a simpler one which can then be controlled by the normal defensive mechanisms of the peritoneum The added use of sulfadiazine, chloromycetin, or streptomycin contributes further to the control of the infection by their action on the gram-negative or other penicillin-resistant organisms.

The diminished incidence of necrotizing infections and cellulitis developing postoperatively in the wounds of patients receiving large doses of penicillin is further evidence of its effectiveness.

INFECTION OF ABDOMINAL OPERATIVE WOUNDS

This same group of organisms may cause infection of abdominal operative wounds. It is minimized by sharp dissection, protection of the wound edges, the use of gauze protection during the operative procedure, burial of a minimum

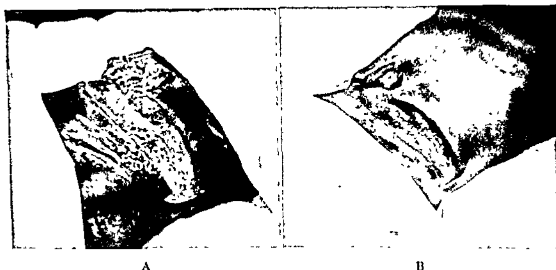


amount of sutures, and closure of heavily contaminated wounds with silver wire sutures through all layers, according to the method advocated by Reid, Zinninger, and Merrill If a wound infection develops, it usually becomes manifest within five to seven days by local swelling, pain, redness, fever, and leukocytosis (Fig. 17).

Control of this type of the infection is dependent upon its early recognition, adequate decompression by incision and drainage to minimize the effect of local factors favoring further spread of the infection and destruction of tissue, adequate chemotherapy with penicillin and sulfadiazine, and removal of obviously devitalized tissue or slough which invites or supports bacterial growth. Streptomycin, bacitracin, aureomycin, and chloromycetin may be of value. Chemotherapy has aided in the control of the invasive qualities of the infection but has not replaced in any sense the principle of early and adequate surgical drainage.

Acute Non-Clostridial Crepitant Cellulitis

Acute non-clostridial crepitant cellulitis is an infrequent clinical entity, characterized by a rapidly spreading, emphysematous infection involving the



A B

Fig 18 —(A) Extensive, acute, crepitant, non-clostridial cellulitis of abdominal wall developing postoperatively after resection of gangrenous ileum strangulated in femoral hernia. Note the epifascial nature and extent of this lesion. Radical incision and drainage have been done and chemotherapy started. (B) The infection has been controlled for the clean granulating surface of same wound The area, now ready for skin grafting fifteen days later, is illustrated.

skin and subcutaneous tissues and accompanied by severe toxemia. The lesion essentially is a rapidly spreading necrotizing infection of the skin and epifascial connective tissues usually occurring in the abdominal wall, perineum, buttocks, hip, thorax, or neck It may occur in wounds after operations for acute secondary peritonitis or resections of portions of the gastro-enteric tract (Fig. 18).

Crepitation usually becomes evident within two to five days after the onset of the infection The lesion appears to be a mixed infection, no single type of etiologic agent being consistently present Again, the various types of organisms recovered from these cases suggest their symbiotic and synergistic relationship Bacteria apparently capable of producing this infection include *B. coli*, anaerobic streptococci, and the anaerobic gram-negative bacilli of the bacteriodes group such as *Bacillus melaninogenicum* and *Bacillus thetoides* The clinical course is characterized by the rapidity of extension of the process, almost

one-half of the wall of the torso becoming involved within four to five days in some instances. Early *diagnosis is essential for effective treatment and the* prognosis is excellent in those patients treated promptly and adequately. The principal method of treatment for this condition is early and adequate surgery, consisting of radical decompression of the involved area by long and wide incisions through the skin and subcutaneous tissues down to the superficial layer of the deep fascia, and peripherally into healthy tissue beyond the furthermost limits of the lesion. Chemotherapy is recommended only as an adjuvant to

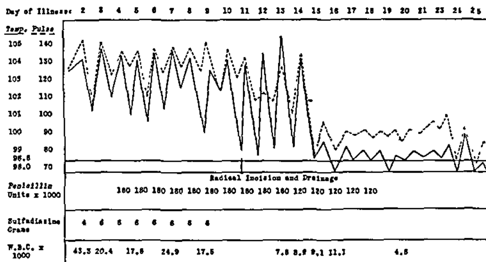


Fig 19—R J, 25-year-old colored female admitted to the Cincinnati General Hospital on January 18, 1945 with acute crepitant non-clostridial cellulitis of the abdominal wall and right flank arising from an injury of the perineum three days earlier Although treated with penicillin and sulfadiazine, the infection was not controlled until radical incision and drainage were performed

surgery (Fig 19) Because of the mixed bacterial flora, parenterally administered penicillin in doses of 50,000 to 100,000 or more units every two hours is recommended, along with 1 gm of sulfadiazine every four to six hours or 200 mg. of streptomycin or dihydrostreptomycin every four hours The value of chloromycetin and aureomycin in this condition has not been established. Daily dressings of the wounds with zinc peroxide ointment may aid in the control of the infection Fever, elevation of the pulse rate, and signs of toxemia frequently persist for three or more days after surgical incision and drainage. After the infection has been controlled and clean granulation tissue has developed within the wound, skin grafting should be done at the earliest opportunity. General supportive therapy is important, including intravenous fluids for adequate hydration and electrolyte intake, repeated whole blood transfusions, and rest

Human Bite Infections

Severe infections with marked morbidity may complicate wounds produced by human bites The infection usually occurs when a human being voluntarily bites another or strikes a blow, his hand thereby being cut by the tooth of the intended victim The wound is usually a puncture wound of considerable

depth through skin, subcutaneous tissues, fascia, tendons, and often into a joint. Since the wound is made with a relatively dull object, contusion of the tissues occurs which supports the growth of the contaminating mouth organisms. A mixture of bacteria is usually found consisting of aerobic nonhemolytic streptococci, anaerobic streptococci. *B melaninogenicum*, spirochetes, and staphylococci. Although spirochetes are never found alone in these infections, they are associated with the more severe ones. In some instances Actinomyces may contribute to the infection.

When fresh human bite wounds are treated by limited or inadequate surgical measures, evidence of inflammation around the bite appears within the first one to three days after injury and progresses steadily thereafter. The part becomes swollen, red, painful, and useless. Fever is usually moderate, but may be as high as 105°F. Systemic reaction is occasionally profound and the appearance of the local infection soon becomes alarming. Granulation tissue forming within the wound becomes shaggy, gray, cyanotic, and edematous. It exudes a thick, foul, and purulent material There is extensive progressive necrosis of tissue, particularly of the areolar tissue Burrowing into the deeper soft tissue spaces as well as the joints is a characteristic of the infection.

The prevention of infection in this type is still the most effective form of treatment. Radical excision of the wound as soon as the patient is seen, followed by zinc peroxide dressings incorporating a splint for immobilization, and combined general sulfadiazine and penicillin therapy are the most effective means of preventing human bite infections. When tendons are severed by tooth wounds, primary tenorrhaphy should not be attempted.

When infection has already occurred, most surgeons agree that any temporizing measure is unsuccessful. Decompression of the infected area and the tissue planes by surgical incision is extremely important. Systemic chemotherapy with sulfadiazine and penicillin, both pre- and postoperatively, is a valuable adjunct to adequate surgical management in the control of this lesion. The recent decrease in morbidity of this lesion can be largely attributed to the effect of antibacterial agents. With the use of penicillin, amputation of the involved finger is almost never necessary.

Tetanus

A clinical study of 35 cases of established generalized tetanus seen in and about Cincinnati has failed to show evidence of the beneficial effect of penicillin or any other chemotherapeutic agent on the course of this disease. *In vitro* studies indicated that penicillin has no effect on the tetanus toxin. The evidence indicates that the successful management of established tetanus depends not on chemotherapy but on early diagnosis, adequate serotherapy for neutralization of free toxin, control of the convulsions, and the administration of general supportive measures. Penicillin is usually employed in tetanus, however, to control secondary wound infections or pneumonia. The most effective treatment of tetanus is still its prevention This may be accomplished by passive immunization at the time of injury with prophylactic injection of 1500 or more units of antitetanic serum Active immunization may be produced by a series of tetanus alum-precipitated toxoid injections which are given subcutaneously and must have been admin-

istered several months before injury occurs. A booster dose of toxoid at the time of injury is desirable.

Gas Gangrene

Gas gangrene is another clinical entity of multiple bacterial etiology. It is a mixed infection which may complicate civilian or military wounds of violence. Principally involving muscle, it is characterized by a spreading, infectious, crepitant gangrene and marked toxemia. It is more common in compound fractures than in soft tissue wounds. A great variety of gas-producing anaerobic bacteria, chiefly the *Cl welchii, Cl. sporogenes, Cl oedematiens, Cl. histolyticus*, and vibrion septique, has been repeatedly found in association with this condition. The individual case usually presents a mixed bacterial flora of aerobes as well as anaerobes, and the clinical picture varies with their combined characteristic activities

Penicillin is the chemotherapeutic agent of choice in the treatment of gas gangrene, streptomycin and polymixon being of no practical value according to our experimental studies Sulfadiazine is moderately effective, and parenterally administered chloromycetin has shown considerable promise in experimental gas gangrene.

The therapeutic value of penicillin has been determined experimentally. Average doses had no measurable effect, but large doses corresponding to approximately 1,000,000 units in an adult every three hours had a very definite effect, reducing the mortality, prolonging the life of the animal, and localizing the lesions With surgery, however, discontinuation of penicillin was followed *by prompt spread of the lesion and ultimate death. Bacitracin had a similar effect* on the control of experimental gas gangrene, but nephrotoxic effects were observed in the kidneys with the high doses required

In 12 consecutive cases of clinical gas gangrene which we have seen, the use of large doses of penicillin in conjunction with surgical decompression or amputation seemed to be of definite value in overcoming the invasive manifestations of the infections, and all cases recovered In general, the massive doses of penicillin permitted surgery to be effective, even in the far advanced and extensive lesions which had spread onto the torso, fewer radical surgical procedures with amputations were necessary at lower levels, secondary pyogenic invaders were inhibited and greatly reduced the mortality rate. If the diagnosis was made at an early stage while the gangrene was more or less localized and incipient, radical decompression of the involved fascial compartments by free longitudinal incisions and excision of the infected muscle usually resulted in arrest of the process and the saving of the extremity. It must be remembered that the early diagnosis of gas gangrene is difficult. It may be unrecognized until the lesion is far advanced, because wounds prone to develop gas gangrene are extensive ones and their treatment requires the use of large dressings, casts, or splints. Observations are thus indirect and deductions as to the progress of events within the wound difficult and uncertain Once the lesion is sufficiently established to permit a diagnosis from the clinical appearance, a far advanced and often irreversible process is present If diagnosis is made late when the process has become extensive and caused irreversible gangrenous changes in the extremity implying

loss of function of the limb (Fig. 20), open amputation of the guillotine type or some modification thereof becomes necessary. The use of adequate amounts of specific antitoxin may aid somewhat in controlling the profound toxemia. Daily blood transfusions should be given for correction of the profound anemia which frequently is associated with this condition and for general supportive effect. Adequate administration of fluids and electrolytes is indicated to correct the accompanying acidosis and toxemia



Fig. 20 – C.W., colored male, age 16, with fulminating gas gangrene developing 24 hours after shotgun injury to left thigh. At operation, gangrenous changes distal to injury were irreversible, and dissecting infection had already spread to abdominal wall. Treatment with open amputation, radical incision and drainage, massive doses of penicillin, and specific serotherapy brought infection under control in spite of its spread into the abdominal wall.

Actinomycosis

Actinomycosis has always been resistant to treatment, particularly when it is of the thoracic, abdominal, or osseous types. Produced by the *Actinomyces bovis*, this infection is characterized by the development of chronic, stony hard, granulomatous masses which subsequently break down to form central abscesses and multiple sinuses. The tumor in time becomes adherent to the overlying skin which then assumes a bronze or purplish-red color. The process exhibits a strong tendency to invade practically all types of tissue other than lymphatic, including the subcutaneous tissues, skin, periosteum, bone, lung, pleura, intestinal tract, etc.

The disease manifests itself during early adult life, usually as one of three types: (a) cervicofacial, (b) thoracic, or (c) abdominal.

In the past, the successful management of this disease depended primarily upon surgical excision of early lesions, x-ray therapy, and/or sulfonamide therapy

in full dosage over prolonged periods This type of therapy was generally effective in the cervicofacial type, but ineffective in arresting or controlling the thoracic or abdominal type. The mortality rate in the two latter types was extremely high and approached 100 per cent once the disease was well established.

Recently the management of actinomycosis has been profoundly influenced by penicillin, which has been shown to be much more effective than the sulfona-



A B

Fig 21 —Illustrating the profound effect of chemotherapy on a case of far advanced thoracic actinomycosis (A) C C, 12-year-old white female with extensive thoracic actinomycosis of two years' duration The entire right side of the thorax is invaded by granulomatous masses. Axillary-tracheo-esophageal fistula is present. The clavicle is bisected by actinomycotic erosion (B) The same patient, 18 months after penicillin and prolonged sulfonamide therapy Note the spontaneous and apparently complete resolution of the infectious process which has occurred. Patient has remained well five years without evidence of recurrence

mides Bacitracin also is of value in the treatment of this infection, although the number of cases successfully treated is relatively small In our experience, penicillin has been most effective when used in conjunction with sulfadiazine or sulfamerazine. Penicillin may be given in the aqueous form in doses of 25,000 to 30,000 units every three hours or in the repository form in doses of 300,000 or 400,000 units every 24 hours over a prolonged period of four to eight or more weeks. The preparations combining 100,000 units of aqueous penicillin and 300,000 units of procaine penicillin should be satisfactory in this condition. Sulfadiazine may be given orally during the same period in doses of 1 gm every four to six hours under careful control by laboratory tests Thereafter, it is often advisable to continue the administration of sulfadiazine for an additional four to 12 months or more in decreased dosage

In our last 23 consecutive cases of actinomycosis, only 2 deaths have occurred; both of these were patients who refused to remain in the hospital long enough to receive adequate chemotherapy. If abscesses or areas of necrosis develop in actinomycosis, incision and drainage should be instituted as usual. The results of combined chemotherapy of the cervicofacial type have been impressive, clinical cures apparently occurring within three to 12 weeks after the beginning of therapy. In the thoracic types, the results of treatment in some instances have been spectacular (*Fig.* 21). Spectacular regression of the process occurred with

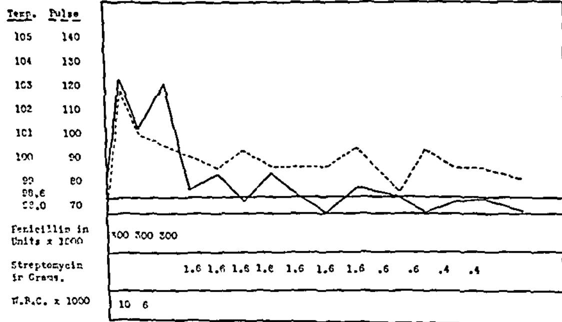


FIG. 22 —K D, 38-year-old white female with recurrent ascending cholangitis developing three years after fourth plastic operative procedure for stricture of common duct. Penicillin and sulfadiazine had been given without effect for four days before her admission to the hospital. Response to streptomycin was prompt.

progressive decrease in size, diminished amount of discharge, and ultimately disappearance of the lesion. Whether or not complete cures have been obtained remains to be seen

CHOLANGITIS

Cholangitis usually occurs as the result of partial obstruction of the common bile duct with ascending infection of the biliary ducts through the stagnant bile or via the lymphatic vessels Occasionally it may occur as a hematogenous infection When infection occurs, it is associated with chills, spiking fever, jaundice, and suppression of the excretion of bile.

Streptomycin is the chemotherapeutic agent of choice in the majority of these cases, being superior to penicillin or sulfadiazine (Fig. 22). It will be interesting to learn of the effect of chloromycetin and aureomycin in the treatment of this condition The dose of streptomycin recommended in the adult is 2 or 3 gm.

daily, given in divided doses every four hours for five to 10 days, depending upon the course of the disease. Since this infection is most apt to develop when some form of obstruction is present in the biliary tract or when the choledocho-intestinal junction no longer is controlled by sphincter action, the importance of surgical correction of the predisposing factors is obvious. If bacteremia is associated with cholangitis, streptomycin in the same dosage generally will cause the organisms to disappear promptly from the blood.

Pylephlebitis

Pylephlebitis is an inflammation of the portal vein secondary to acute inflammatory disease of the gastro-enteric tract Septic thrombosis of the portal vein or its tributaries is frequently present The clinical picture is striking, being characterized by the sudden onset of severe bed-shaking chills, marked prostration, tachycardia, septic fever, malaise, anorexia, vomiting, and frequently jaundice Multiple small abscesses usually develop throughout the liver as the infection extends into the portal tributaries within the liver. The infection is extremely severe and the mortality rate approaches 100 per cent. An associated bacteremia due to *B coli* or *A aerogenes* frequently is present.

At the present time, chemotherapy offers the only hope for the great majority of these patients, and streptomycin, chloromycetin, and aureomycin are the drugs of choice However, cultures of the septic thrombi within the vein and of the abscesses within the liver usually indicate the presence of a mixed infection, consisting of both gram-negative and gram-positive organisms. Consequently, the administration of penicillin or sulfadiazine in addition to streptomycin is recommended The dose of streptomycin which has usually been used in this condition is 2 to 3 gm daily divided in four or six doses given intramuscularly over a period of 10 to 21 days

Tuberculous Infection

Antibacterial therapy of tuberculous infections should not be considered a definitive or adequate method of treatment Streptomycin, however, has demonstrated its ability to produce marked therapeutic benefits in patients with some types of tuberculosis The dangers of streptomycin toxicity have been reduced by reduction and regulation of its dosage and by its chemical alteration to dihydrostreptomycin The latter compound is distinctly less toxic, but apparently possesses the same therapeutic properties as the former Hence, dihydrostreptomycin is the chemotherapeutic agent of choice, although it must be remembered that it can also produce toxic manifestations.

Streptomycin appears to be most effective in the management of recent and acute tuberculous lesions, and its use is particularly recommended for the treatment of tuberculous pneumonia, miliary tuberculosis, tuberculous peritonitis, and tuberculous meningitis According to the Clinical Subcommittee of the Committee on Medical Research and Therapy of the American Trudeau Society, the administration of streptomycin is recommended especially for the following types of pulmonary tuberculosis: (1) acute bronchopneumonic tuberculosis with marked symptoms, (2) acute bronchogenic spread; and (3) chronic disseminated

nodular tuberculosis without confluent areas of destructive disease. Usually, the effectiveness of streptomycin is proportional to the extent of the acute portion of the disease active at the time of chemotherapy.

In generalized miliary tuberculosis without meningeal infection, treatment with streptomycin is certainly indicated, and it should be instituted as early as possible. The success of this type of therapy in disseminated tuberculosis will ultimately be determined by the percentage of three- to five-year survivals.

In tuberculous meningitis, dramatic remissions may follow the use of streptomycin, but the mortality has not been greatly decreased as yet.

Tuberculous sinuses of the skin and adjacent soft tissues have responded well to streptomycin treatment and recurrences have been relatively infrequent. Tuberculous lymphadenitis usually becomes quiescent. Old tuberculous pleural and anal fistulas are usually refractory to chemotherapy.

Antibacterial treatment with streptomycin has been effective for ulcerative lesions of the nasopharynx, larynx, middle ear, and trachea. Therapy is usually followed by relief of pain within one week and healing within two to six weeks. In tuberculous enteritis the results have been uniformly favorable. Lesions of the genito-urinary tract may respond well. Sinus tracts and ulcerations of the bladder may heal, but there is seldom any change in the degree of renal damage.

Streptomycin has a limited but favorable effect on tuberculous infection of bones and joints, particularly when used in conjunction with surgery. Antibacterial therapy has not changed the prognosis of tuberculous lesions of the brain.

It must be emphasized, however, that the greatest usefulness of streptomycin therapy has been in conjunction with other forms of treatment such as rest in bed, collapse therapy, and surgery. Because streptomycin can be used for periods of only two to four months in patients with this disease, and because of the development of resistant organisms, it is obvious that streptomycin should be used at the time when the greatest benefit will be realized. The timely integration of chemotherapy with other established methods of treatment to selected patients is advocated.

Another benefit of chemotherapy has been the increased possibilities for the surgical treatment of pulmonary tuberculosis. The reduction of toxemia, improvement of the patient's general condition, and resolution of acute exudative lesions, particularly of the opposite lung, have made thoracoplasty or pulmonary resection possible for larger numbers.

Streptomycin is administered intramuscularly, but not topically except in the case of meningitis, when intrathecal injections are advisable. The most effective dose and period of treatment are still undetermined. A dose of 0.5 to 1 gm. given once daily is generally used at the present time, although doses of 2 to 3 gm daily are given by some surgeons. Curiously, there is no satisfactory explanation of the effectiveness of streptomycin when given in such small doses at such prolonged intervals.

The use of a combination of antibacterial agents, such as promin and para-amino-salicylic acid, may postpone the development of bacterial resistance to streptomycin, and may have an additive therapeutic effect.

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Carcinoma of the Lung

Carcinoma of the Lung

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During the past few decades carcinoma of the lung has steadily increased in importance. This may be accounted for by a number of factors, among the most important of which are (1) the recognition of its relative frequency and apparently increasing incidence, and (2) the gratifying progress which has been made in its surgical treatment. Until Graham's pioneering demonstration only 16 years ago that resection of a pulmonary cancer was possible the disease was considered hopeless. This successful achievement, perhaps more than any other factor, provided impetus toward a better appreciation of the disease. In many respects the developments in this condition reflect the rapid progress which has taken place in this relatively short time in the field of thoracic surgery.

INCIDENCE

It is now recognized that carcinoma of the lung is one of the most common types of malignancy, being preceded in frequency in males only by carcinoma of the gastro-intestinal tract, skin, and prostate. This is a curious reversal of the opinion held concerning its incidence only a few decades ago, and this change from a relatively infrequent to a relatively common malignancy constitutes one of the most interesting features of the lesion. In a monograph on the subject published in 1912, Adler stated that, "there is complete consensus of opinion . . . that primary malignant neoplasms of the lung are among the rarest forms of disease." Since this statement was made the incidence of carcinoma of the lung has risen steadily and at the present time there is general agreement among investigators in all parts of the world that the disease ranks high as a primary form of cancer, comprising from 3 to 5 per cent of all malignancies.

Although there may be some question as to whether this increase in incidence is real and absolute or only apparent and relative, the important practical consideration is that virtually all observers who have analyzed the situation in their institutions have found a steady rise in the occurrence of the disease. Thus, at the Dresden City Hospital the incidence of carcinoma of the lung as based on all malignant tumors observed in postmortem examinations increased fivefold, from 0.92 per cent to 4 66 per cent during the 67 year period from 1852 to 1919. Similar necropsy studies at the University of Leipzig showed that the incidence of carcinoma of the lung among all carcinomas had risen from 5.01 per cent to 9.17 per cent during the period 1900 to 1922. At the Bern Pathologic Institute the incidence of bronchiogenic carcinoma observed at necropsies increased almost sixfold during the period 1900 to 1939 In Buenos Aires at the Institute of Pathological Anatomy of Ciencies Medicus, Loizaga reported an incidence of 5.18 per cent for carcinoma

of the lung among all postmortem carcinomas during the period 1898 to 1917, whereas this incidence during the period 1918 to 1937 was 14.6 per cent. Somewhat similar increases in the incidence of bronchiogenic carcinoma in necropsy series have been reported by numerous other observers abroad as well as in this country.

In an analysis of 5,515 necropsies performed by members of the Department of Pathology of the University of Chicago during the 40 year period, 1902 to 1941, Steiner found 126 (2.3 per cent) cases of primary carcinoma of the lung, comprising 7.6 per cent of all malignant tumors and 10.3 per cent of all carcinomas. Moreover, it ranked fifth in frequency among all types of tumors and third among carcinomas. During the period of this analysis the percentage of lung cancer in all necropsies increased about threefold.

There has also been a steady increase in the death rate from cancer of the lung. Thus Harnett found that, whereas the total number of cancer deaths in the British Empire had increased 22 per cent, cancer of the respiratory tract had increased 120 per cent, and the deaths from cancer of the lung in males from 1921 to 1930 was 21.1 per million, whereas in 1937 it was 100.0 per million. In a more recent report of an analysis of death certificates for cancer of the lung and of the larynx in England and Wales for the years 1921-1938 inclusive, Kennaway found that the incidence during this period had increased by 16.5 times in men and by eight times in women, although the incidence of cancer of the larynx had not risen in either sex during the last 15 years. According to Clemmesen and Busk, official mortality figures in Denmark show an apparent rise in lung cancer, particularly among males. These observers reported an increase since 1931 from about 5 per 100,000 to about 25 per 100,000 in 1945. In this country Dorn found that between 1913 and 1930 the death rate from cancer of the lung increased 3.7 times, whereas during this same period there was an increase of only 20 per cent for all forms of cancer combined. Moreover, the death rate continued to increase from 1930 to 1940 to 22 per cent in white females and 78 per cent in white males, or approximately 2.5 and 8.5 per cent per year, respectively. Dorn further estimates that between 450,000 and 500,000 people in the United States are under medical treatment for cancer, and about 13,000 are being treated for primary cancer of the lung. In a later statistical analysis of cancer in the United States Dorn found that out of every 100 white men who develop cancer 46 will have cancer of the buccal cavity and digestive system, 17 of the urogenital system, 17 of the skin, and 8 of the respiratory system. On the basis of vital statistics reports in the United States for the 10-year period 1936-1945, there was a progressive increase in the number of deaths from cancer of the lung and pleura, while for the same period no significant increase occurred in the death rate for cancer of the stomach and duodenum (Fig. 1).

Our experience at the Charity Hospital in New Orleans reflects this same trend in the occurrence of the disease. During the 10-year period ending December 1946, the annual incidence of carcinoma of the lung in this institution has risen steadily, whereas that of carcinoma of the stomach has shown a slight decrease (Fig. 2). Suggestive of a racial factor is the fact that this increase in incidence occurred primarily among white patients with little or no change among the Negro patients. This observation obtains further support from a comparison of

the racial incidence of carcinoma of the lung and stomach with all admissions. Whereas the ratio of white to Negro patients is about 3:2 for carcinoma of the stomach and perhaps not significantly different from that for all admissions, for

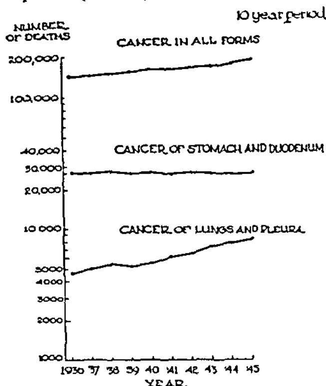


FIG 1 —Comparative incidences of cancer of lung and pleura, of stomach and duodenum, and of cancer in all forms, based upon number of deaths from vital statistics reports in the United States.

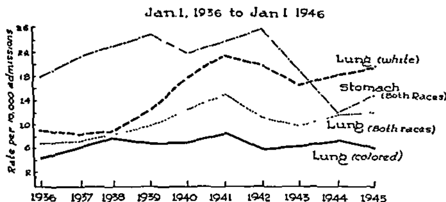


FIG 2 —Comparative incidences of carcinoma of lung and stomach in white and colored races, based upon admissions to the Charity Hospital in New Orleans during the 10-year period 1936-1945, inclusive

carcinoma of the lung, this ratio is practically reversed, being 2:1 in favor of the white race (Fig 3).

Sex Incidence

It has long been recognized that carcinoma of the lung is predominantly a disease of the male sex, although no satisfactory explanation for the sex discrep-

ancy has been advanced. According to available statistics, including our own, the disease occurs about five or six times as often in males as in females (Fig. 4). In a previous report we found that in a series of 8,575 collected cases in which

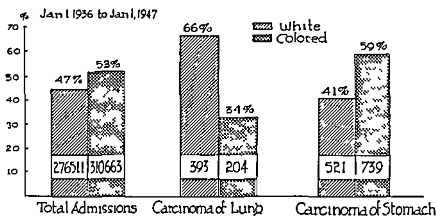


FIG 3 —Racial incidence of carcinoma of the lung and stomach, based on admissions to the Charity Hospital in New Orleans during the 11-year period 1936-1946, inclusive

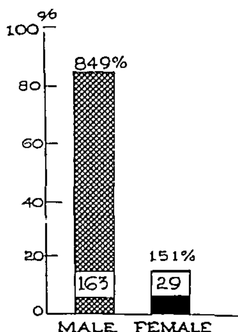


FIG 4 —Sex incidence in authors' series of 192 resected cases of primary pulmonary malignancy

the sex was stated, there were 6,769 males (78 9 per cent) and 1,806 females (21 per cent). According to Dorn, the increase in the death rate from cancer of the lung in the United States during the period 1914 to 1930 was greater among males than females, the relative increases being 4 5 and 2 6 times, respectively. He also found that whereas the average death rate from all forms of cancer is

about 9 per cent higher for females than for males, the rate for cancer of the lungs among males is nearly 2.5 times that among females.

AGE INCIDENCE:

Carcinoma of the lung, like other carcinomas, occurs most frequently in the fifth, sixth, and seventh decades More than 85 per cent of our cases were in this age group, with the highest incidence in the sixth decade (Fig. 5). The youngest patient in this series was 12 years of age and the oldest was 81. In a previously reported series of 4,307 collected cases, arranged according to decades the follow-

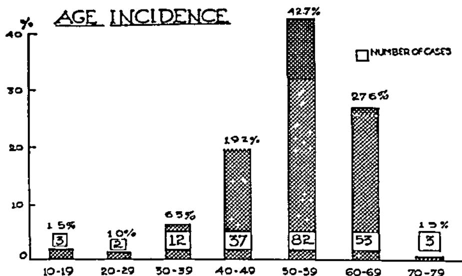


FIG. 5 —Age distribution by decades in the authors' series of 192 resected cases of primary pulmonary malignancy.

ing results were found first decade, 0.16 per cent, second decade, 0.7 per cent, third decade, 2 9 per cent; fourth decade, 10.7 per cent; fifth decade, 25.4 per cent; sixth decade, 34.1 per cent; seventh decade, 20 per cent; eighth decade, 5.4 per cent, ninth decade, 0 58 per cent. Thus, well over half of the patients were between the ages of 40 and 60 and approximately four-fifths were between the ages of 40 and 70 years.

ETIOLOGY

The apparent increase in the incidence of carcinoma of the lung has stimulated much speculation concerning its cause. The numerous explanations advanced to account for this fact have been reviewed in previous publications. They include particularly such factors as occupation, smoking, inhalation of irritating dusts and fumes, and previous pulmonary infections. In the analysis of our cases none of these factors was found to bear a significant relation to the occurrence of the disease. Both occupation and smoking, which have been particularly emphasized by some observers as possible etiologic factors and which we were inclined previously to consider more seriously, were found to have no special significance in this analysis. Perhaps the most significant factor that has been found to affect

the occurrence of the disease is the inhalation of radioactive substances. This is exemplified by the high incidence of carcinoma of the lung among workers in certain mines in which demonstrable radioactive dust exists. Thus in the Schneeberg mines, 62 per cent of workers who were followed until death died of primary carcinoma of the lung. Similar observations have been made among workers in the pitchblende mines of Joachimsthal, which is across the mountains from Schneeberg More recently another type of occupational hazard has been found to bear a significant relationship to the occurrence of carcinoma of the lung This concerns the chromate-producing industry in which an analysis of the mortality [illegible]

[illegible] per cent of all deaths were due to cancer of the respiratory system, which is 16 times the expected ratio They also found that the crude death rate for cancer of the lung was 25 times the normal and that the mortality rates for lung cancer in the group 50 years of age and under ranged from 20 to 70 times that for a comparable industrial group, and for those over 50 years it ranged from 10 to 40 times that for a comparable industrial group Their data suggest that the monochromates may be the compounds responsible for lung cancer.

PATHOLOGY

Most primary tumors of the lung are malignant, and with few exceptions they are bronchiogenic in origin. One of these exceptions is the diffuse primary alveolar carcinoma of the lung, also referred to as cystic papillary lung tumor, pulmonary adenomatosis, mucous epithelial hyperplasia, and alveolar cell tumor of the lung Although there is some controversy concerning the origin of these tumors, the evidence suggests that they are probably derived from living alveolar epithelial cells Grossly two forms of the disease may be recognized, the diffuse form, indistinguishable from lobar pneumonia in the state of so-called gray hepatization, and the nodular form Microscopically the lesion is characterized by alveoli-lined, *tall, columnar, mucus-secreting cells many of which show papillary infolding* This form of the disease also differs from the more common type of bronchiogenic carcinoma in that it occurs with equal frequency in both sexes. Other forms of primary pulmonary malignancies also occur relatively rarely. In a previous analysis of 195 resected cases of primary neoplasms of the lung, the lesions were found to be carcinoma in 191 and in the remaining 4 cases, one was a neurofibrosarcoma, one Hodgkin's disease, one lymphosarcoma, and one malignant melanoma.

Site of origin in carcinoma of the lung is often difficult to determine. Its location at the time of examination may represent only the stage of the process. Barnard believes that carcinoma arises most frequently at the junction of the bronchial branch with its parent stem In general, it would appear from the figures on the site of involvement that this is a reflection of the relative size of the various lobes of the lung Thus the right lung, which is the larger, is involved somewhat more frequently than the left. In a previously collected series of 4,732 cases, 58 3 per cent involved the right lung and 41.6 per cent the left lung. These percentages correspond closely with those obtained in our resected series

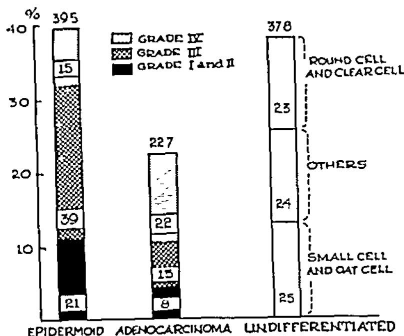


FIG 6.—Distribution by histologic type and grade of the authors' series of 190 resected cases of carcinoma of the lung.

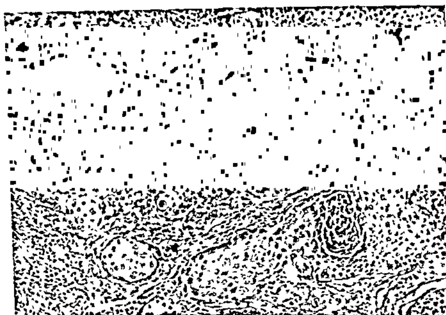


FIG 7—Epidermoid (squamous cell) carcinoma of the lung, grade II, showing a few small epithelial pearls

and those reported by Bjork The two upper lobes and the right lower lobe were involved with approximately equal frequency, i e., about 24 per cent, while the incidence of involvement in the left lower lobe was about half this figure. These figures are not much different from those reported by Björk. The fact that the upper lobes in our operative series were involved so frequently is significant, for,



FIG 8 —Adenocarcinoma of the lung, showing low columnar and cuboidal tumor cells forming irregular gland-like spaces in the fibrous stroma, with small papillary projections of the tumor extending into the lumen of these spaces

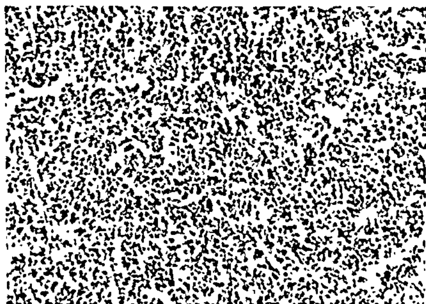


FIG. 9 —Undifferentiated carcinoma of the lung, small round cell type, showing fairly uniform small, round, dark-staining cells without any distinctive arrangements

as will be pointed out later, this adds to the diagnostic difficulties of bronchoscopy. In approximately half of our cases the lesion was situated peripheral to the lobe bronchi and only about 8 per cent were in the main stem bronchi.

There have been numerous classifications of carcinoma of the lung, based usually on the histologic or morphologic appearance of the tumor In the analysis

of our cases only three major groupings were used (Fig. 6): epidermoid (squamous cell) carcinoma (Fig. 7), adenocarcinoma (Fig. 8), and undifferentiated carcinoma. The first two forms were subdivided into four grades of histologic



Fig. 10.—Undifferentiated carcinoma of the lung, oat cell type.

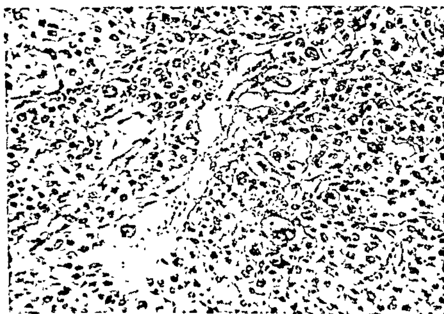


Fig. 11 —Undifferentiated carcinoma of the lung, large clear cell type.

malignancy and the undifferentiated forms were divided into three subgroups, according to cell type, first, the small round cell (Fig. 9) and the oat cell carcinoma (Fig. 10), second, the large round cell and clear cell tumors (Fig 11); and third, a miscellaneous group of irregular cell types (Fig. 12) The squamous cell

carcinomas are characterized by a tendency toward keratinization or pearl formation with central keratinization. The adenocarcinomas are composed of cuboidal or columnar cells forming tubular or acinar structures with gland-like spaces in the fibrous stroma or are mounted on delicate connective tissue stalks in a papillary arrangement. The small round cell type of undifferentiated carcinomas consists of rather uniform, small, round, dark staining cells which have no definite pattern of arrangement. Differentiation of this tumor from lymphosarcoma may be made by careful attention to the structure of the nuclei and to the occasional

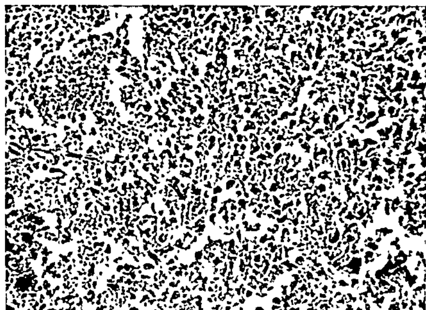


Fig 12 —Undifferentiated carcinoma of the lung, representing the heterogenous group of these tumors which are not subclassified.

not considered as an undifferentiated type. These tumors have been classified by some observers as sarcomas, but occasional transitions to definite epithelial structures have been noted in numerous sections In the large clear cell type of undifferentiated carcinoma there are usually a few attempts to form gland-like structures or small nests of keratinized cells Finally, the unclassified, undifferentiated carcinomas consist of a heterogenous group of tumors with irregularly shaped cells.

Metastasis in carcinoma of the lung is characterized by widespread distribution. This is probably a consequence of a number of factors including the invasive powers of the tumor, the ready and ample facilities for its becoming blood-borne, and the abundant lymphatic supply of the lungs. A detailed consideration of this phase of the subject has been presented elsewhere. The modes of extension may be listed as follows: (1) direct extension, (2) bronchial intraluminal extension, (3) hematogenous, and (4) lymphatic. Direct invasion of contiguous structures

is obviously a frequent method of extension, as in malignancies elsewhere, but its relative significance in cancer of the lung is particularly great because many of the neighboring structures in this area are vital organs which cannot be extirpated if invaded. Invasion by this means is one of the most common causes of inoperability. Bronchial intraluminal extension or the so-called aerogenous route, sometimes referred to as surface spread, probably occurs relatively infrequently. In those cases in which the primary lesion originates proximally, this method may in some instances be responsible for peripheral involvement of the same lung or the opposite lung. The hematogenous route of metastasis is one of the most important because of its frequency and its responsibility for widespread distribution to such organs as the brain, the liver, the kidneys, and the adrenals, and to the bones. This method of extension is more liable to occur in carcinoma of the lung than in malignancies of other organs because the filtering barrier is absent.

The overwhelming preponderance of regional lymph node involvement attests to the importance of the lymphatic route of metastasis. According to Rouvière, the collecting trunks of the lymphatics of the lung may be divided into three principal regions, depending upon the lung areas drained: (1) superior, (2) middle, and (3) inferior. The superior lymphatic region is formed by the superior and larger part of the upper lobes, and the collecting vessels of this area drain into the laterotracheal lymph nodes The middle lymphatic region on the right is formed by the posterolateral portion of the upper lobe, the entire middle lobe, and the superior part of the lower lobe, and on the left it is formed by the smaller inferior part of the upper lobe and the superior and middle portions of the inferior lobes. These collecting vessels drain into the laterotracheal and intertracheobronchial nodes. The inferior part of the lower lobes forms the inferior lymphatic region and the collecting lymphatics of this area drain into the intertracheobronchial nodes. A further pathway of lymph drainage from the lungs exists in the ligamentum latum pulmonis which extends from the lower lobes of both lungs. These lymph-collecting vessels reach a retro-esophageal supradiaphragmatic node which is connected by an efferent transdiaphragmatic trunk to an abdominal juxta-aortic node It is evident from this brief description of the lymphatic system of the lungs that ample pathways exist for widespread dissemination of metastases. This fact is also of particular surgical significance. Since the lymphatic drainage of the pulmonary lobes does not entirely conform to the anatomic divisions of these lobes, extirpation of possibly involved nodes necessitates their dissection in the mediastinum

The most frequent sites of metastatic involvement are the regional lymph nodes in the peritracheobronchial and mediastinal areas Lymph-borne metastasis occurred in 66 per cent of Bjork's series. In a series of 3,047 collected cases which we previously reported, the regional lymph nodes were involved in 72.2 per cent. The spread of cancer of the lung by the lymphatic route, however, is not limited to these nodes While in a collected series of 1,298 cases in which the metastatic sites to lymph nodes were stated, the tracheobronchial nodes were involved in about 70 per cent, there was a wide range of involvement in the remaining 30 per cent. Among the latter the abdominal nodes were the most commonly involved and following these in order of frequency were the cervical, retroperitoneal, iliac,

axillary, peripancreatic, supraclavicular, peribiliary, submaxillary, and inguino-femoral nodes.

Next in frequency to the regional lymph nodes as site of metastatic involvement is the liver. In our collected series this was observed in 33.3 per cent, which is a relatively high incidence and may be explained on the basis of both hematogenous and lymphatic extension. The pleura and lung form the next most frequent sites of metastasis, and metastases were found in these sites in 29.8 and 23 3 per cent, respectively, of our collected series. The next most frequent sites of involve-

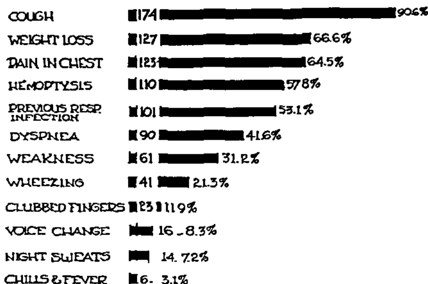


FIG 13 —Comparative incidence of recorded symptoms among the authors' series of 192 resected cases of primary pulmonary malignancy.

ment in our series were as follows bone, 21.3 per cent; adrenals, 20.3 per cent, kidneys, 17 5 per cent, brain, 16.5 per cent, heart and pericardium, 12.7 per cent

CLINICAL MANIFESTATIONS

The clinical picture of carcinoma of the lung is unfortunately not sharply characteristic, especially in its early stages. This fact, in addition to the usually insidious onset, probably accounts in good part for the frequent delay in diagnosis In our experience the most frequent manifestations are cough, loss of weight, pain or discomfort in the chest, a history of a previous respiratory infection, hemoptysis, and dyspnea, in about that order of frequency (Fig 13). The next most frequent manifestations are weakness, wheezing, clubbed fingers, voice change, night sweats, and chills and fever. Not infrequently, only one or two of these manifestations are present, and occasionally the patient has no symptoms,. the diagnosis being made from a routine roentgenogram of the chest.

Cough, which is by far the most common complaint and often the earliest in development, is unfortunately too easily attributed to smoking and accordingly may be disregarded or not properly evaluated For this reason it is important to bear in mind that the cough may not be due to smoking but to an early developing lung cancer, particularly in elderly males and especially if the cough persists,

shows any change in character, or becomes associated with other thoracic symptoms. At first the cough is nonproductive, but later it is accompanied with expectoration. Although at first the expectoration may be scanty and mucoid, it tends later to be more profuse and may become mucopurulent or even foul. It is frequently blood-tinged; *hemoptysis occurred in well over half of our cases and* should be considered a particularly significant sign.

Another incident which is frequently ignored but which may be a valuable clue to diagnosis is the history of a previous respiratory infection. This is especially significant if the patient dates the onset of his present complaints to the

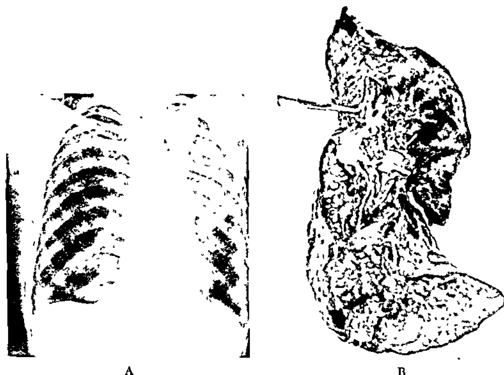


FIG 14 —(A) Anteroposterior roentgenogram of the chest, showing increased density of the left upper lung field with shift of the mediastinum to left, indicating atelectasis of the left upper lobe Bronch
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shows the b
complete occlusion of this bronchus and atelectasis of the lobe beyond it.

occurrence of such an illness and notes persistence of symptoms following the *acute phase of the infection. The full significance of this series of events is fre-*quently not appreciated until several months have elapsed and considerable progression of the malignant lesion has taken place. The frequency with which this occurs emphasizes the need for greater awareness of the possibility of carcinoma of the lung as the cause for such manifestations.

Actual pain in the chest *is relatively uncommon* except as a late sign, but an indefinite pain or a vague discomfort is a frequent complaint, occurring in approximately two-thirds of our cases. Such vague disturbances assume special signifi-

cance if they persist and are not satisfactorily explained on some other basis. Loss of weight may not be appreciable in the early stages but it is usually progressive and soon becomes apparent. Later it is associated with weakness and loss of appetite. Dyspnea is also not an early manifestation but wheezing occasionally does appear fairly early, especially if the lesion encroaches on the lumen of one of the lobar bronchi

The physical findings in carcinoma of the lung are also variable and, like the symptoms, are generally not characteristic, especially in the earliest stages of the

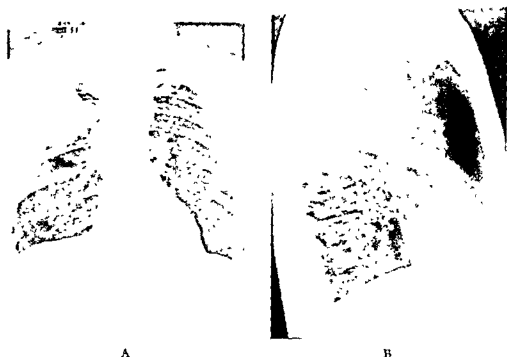


Fig. 15 —(A) Anteroposterior and (B) lateral roentgenograms of the chest showing [illegible] shadow in the peripheral part of the [illegible] manifest[illegible]

disease The nature of the findings depends to a great extent upon the site, size, and direction of growth of the tumor and the consequent secondary pulmonary changes. Significant manifestations are more likely to be encountered if the tumor encroaches on the lumen of larger bronchi or on the pleura. Thus a relatively small tumor completely occluding a main stem or lobar bronchus will produce striking physical findings because of the atelectasis which follows the bronchial obstruction (Fig 14) On the other hand, a peripherally located tumor of considerable size which does not cause obstruction to a major bronchus or encroach on the pleura may produce relatively few physical manifestations (Fig. 15). Limitation of expansion, dullness, decreased breath sounds, and râles occur with great variability and are most frequently present in the late stages. Increasing experience with this disease has emphasized the unreliability of ordinary physical examination as a means of detecting its presence in the early stages.

DIAGNOSIS

The most important factor in diagnosis of carcinoma of the lung is the consideration of its possible presence. With increasing experience we have become more and more convinced that the key to improvement in the early diagnosis of pulmonary cancer lies in the wider recognition and the constant recollection that symptoms referable to the respiratory system, no matter how vague or insignificant they may appear, may be caused by a pulmonary malignancy. This is particularly true in males over 40 years of age, and the diagnosis should always be suspected in such individuals with a persistent cough, unexplained thoracic discomfort, or hemoptysis.

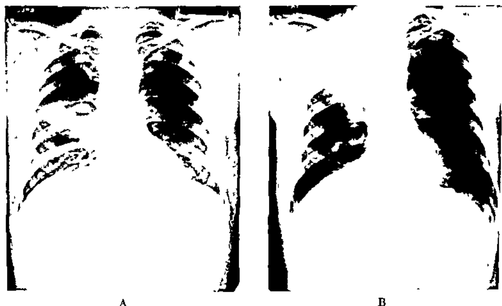


FIG 16A.—Anteroposterior roentgenogram of the chest, showing an irregularly shaped hilar shadow on the left side This patient's symptoms began one year prior to admission and earlier films showed "slightly increased hilar markings" not considered significant, and a subsequent diagnosis of "unresolved" pneumonia was made Bronchoscopy was "negative."

The most important diagnostic procedures include roentgenography, bronchography, bronchoscopy, and cytologic examination of the sputum or bronchial secretions Roentgenography is one of the most useful diagnostic aids in providing suggestive evidence of bronchiogenic lesions, such information was obtained in about 85 per cent of our cases. It should be the initial step in the diagnostic routine in every suspected case. It should be realized, however, that in early nonobstructing lesions the roentgenogram may show little or no change, especially if the lesion is centrally located where the difficulty of interpretation is increased by confusion with hilar shadows produced by other lesions or by normal structures (Fig 16) In this early stage serial roentgenograms, which will reveal an increase in the size of the shadow as the tumor grows, are particularly valuable (Fig. 17) It may also be possible in this way to distinguish hilar shadows produced by a centrally located lesion from those caused by normal structures Occasionally a routine roentgenogram will reveal a bronchiogenic carcinoma in a patient who has no thoracic symptoms or signs and in whom no pulmonary



FIG 16B —Same case as shown in Fig. 16A At operation, pneumonectomy was performed and the gross specimen showed the lesion arising from the upper lobe bronchus and producing nodular projections on the mucosal surface There was metastatic involvement of the tracheobronchial lymph nodes The patient died of recurrence one and a half years after operation.



A B

FIG 17 —(A) Anteroposterior roentgenogram of the chest, showing a roughly triangular area of increased density in the right mid-lung field The diagnosis at this time was "unresolved" pneumonia, the patient had not completely "recovered" from an upper respiratory infection and associated pneumonitis which had begun two months earlier (B) The roentgenogram four months later revealed virtually complete involvement of the left upper lobe, but much of this apparent
h resultant
was con-
nal nodes

neoplasm is suspected. This occurred in 7 patients among our 195 cases in which pulmonary resection was done for cancer of the lung. Our experience as well as that of others emphasizes the great value of roentgenography as part of the routine medical examination of all men in middle life and beyond.

Thorough roentgenographic examination should include fluoroscopy, exposures in various positions, and, in some cases, spot films, grid films, tomography or the so-called "body section" technics. The character of the roentgenogram in carcinoma of the lung varies considerably and depends upon the site, size, and type of lesion. A relatively small lesion, if it occludes a large bronchus, can produce a large opaque shadow. In such an instance the opacity largely reflects the



FIG 18A [illegible] of the chest, showing an extensive area of increased density [illegible]

extent of the consequent atelectasis and need not be interpreted as necessarily representing actual pulmonary invasion by the neoplasm to that extent (Fig. 14). In fact, atelectasis due to bronchial obstruction, either segmental or lobar, accompanied by varying degrees of pneumonitis, constitutes one of the most common roentgenographic findings in carcinoma of the lung Among 231 cases studied by Bjork, an atelectasis was found in 68.8 per cent. In other instances, however, the roentgenogram may provide good evidence of the actual extent of the lesion (Figs 18 and 19) In still other instances the picture is suggestive of a lung abscess (Fig. 20). This may be a consequence of the stasis produced in an area of the lung drained by a bronchus which is occluded by the tumor or of interference with the blood supply in the center of a rapidly growing tumor which results in necrosis and infection Indeed, the occurrence of a lung abscess in a man past 40 years of age which cannot be satisfactorily explained otherwise should always arouse suspicion of an underlying malignancy. This is emphasized by the findings of Brock and of Bjork The former, in an analysis of 363 cases of lung abscess found

that 47 (13 per cent) were due to carcinoma. The latter observed that among the 44 cases of well defined rounded tumors in his series of bronchiogenic carcinomas there were 10 (23 per cent) that showed cavitation on the roentgenogram



FIG 18B—Same case as shown in Fig 18A Although this is an extensive tumor, at operation it proved to be resectable.

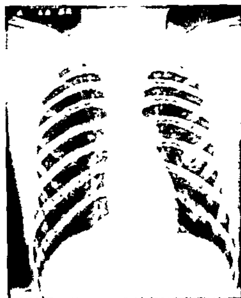
and among the entire series of 231 cases of pulmonary cancer 22 (9 5 per cent) showed roentgenologic evidence of abscess of the lung. Such cases are at times diagnosed in the roentgenogram by an irregularity of the wall of the abscess giving evidence of the extension of the neoplastic tissue into the abscess cavity Tomographic examination in these cases is of particular value because it provides better visualization and sharper delineation of the walls of the cavity. Occasionally a relatively small lesion in the periphery of the lung will produce a large hilar shadow because of involvement of the mediastinal nodes, the shadow produced by the nodes being much larger than that of the originating lesion



Fig. 19A —Anteroposterior roentgenogram of the chest, showing an extensive area of increased density in the right lower lung [illegible]
lobe and intimately adhered [illegible]



Fig 19B —Same case as shown in Fig 19A The gross specimen demonstrates that the right lower lobe has been practically replaced by the neoplasm.





A B

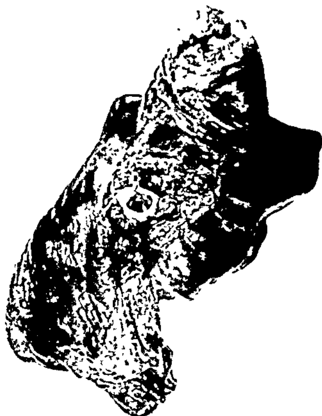
Fig 20 —(A) Anteroposterior roentgenogram of the chest, showing in the left lung a roughly round area of increased density with a central area of diminished density suggestive of lung abscess Following failure of intensive conservative therapy, lobectomy was performed (B) Resected specimen shows the lung abscess Histologic examination proved the underlying lesion to be carcinoma of the lung



Fig. 21A —Anteroposterior roentgenogram, with a localized area of increased density in the apex of the left upper lobe This lesion was first considered to be tuberculous and later suspected of being malignant. Exploratory thoracotomy proved it to be bronchiogenic carcinoma.

In the so-called Pancoast syndrome, produced usually by cancer of the lung originating in the superior pulmonary sulcus, the roentgenogram is fairly characteristic, showing a shadow in the apex of the upper lobe with erosion of the first or second ribs. At this stage the lesion is nonresectable but in some instances an earlier stage of the lesion is observed (Fig. 21).

Bronchography is not an essential or even desirable diagnostic procedure in



[illegible] reveals the [illegible]ld probably [illegible]ain referred

most cases of suspected lung cancer. Occasionally, however, it can provide useful information in certain forms of the disease For example, in lesions located in the periphery of the lung or involving the upper lobar bronchi, which are beyond the vision of the bronchoscopist, or in occasional instances in which suspicious clinical manifestations exist but ordinary roentgenography discloses no significant findings, it can be of diagnostic assistance. In such cases bronchography may permit visualization of an obstruction, narrowing, or other abnormality of the bronchus and thus provide confirmatory evidence of a primary neoplasm.

The most reliable method of establishing a positive diagnosis of bronchiogenic carcinoma is by means of bronchoscopic visualization of the tumor and biopsy of the lesion Unfortunately, the procedure is not applicable in a large group of cases, either because the tumor is located so far peripherally as to be beyond

the vision of the bronchoscopist or because of its location in the upper lobes. Under the latter circumstances, if the tumor is not too far from the opening of the upper lobar bronchus it may be visualized by means of a mirror or a special bronchoscope which permits periscopic visualization, but biopsy of the growth is usually not possible Our experience with bronchoscopy, in contrast to some observers who report incidence of positive bronchoscopic diagnosis as high as 60 to 75 per cent, suggests that it can provide a positive diagnosis of carcinoma of the lung in less than half the cases. In the most recent analysis of our 195 cases of resection for primary pulmonary malignancy it was reported that bronchoscopy was done in 161 (82.6 per cent) and not done in the remaining cases because the lesion was located so far peripherally that it obviously could not be visualized. Of the 161 cases submitted to bronchoscopy a biopsy was obtained in 100 Histologic examination showed evidence of malignancy in 74. Thus, positive evidence of malignancy by bronchoscopic biopsy was obtained in about 46 per cent of the cases in which bronchoscopy was performed, and in only 38 per cent of the entire series. Careful pathologic examination of the resected lungs provided a ready explanation for this relatively low incidence. In approximately half of the cases the lesion was situated peripherally to the lobe bronchi. The chance of bronchoscopic visualization of the more centrally located tumors is further reduced by the fact that a large proportion originates in the upper lobe bronchi beyond easy range of bronchoscopy. It becomes apparent, therefore, that bronchoscopy has definite limitations as a procedure for establishing a positive diagnosis of pulmonary cancer and that a large proportion of patients with this disease would be denied proper treatment if operation were limited to those in which a positive biopsy is obtained It should be recalled, however, that even in cases in which it cannot provide a positive diagnosis, bronchoscopy may be of considerable value to the surgeon in determining the extent of the lesion and the consequent planning of the surgical treatment For example, integrity or paralysis of the vocal cords, compression, displacement, or fixation of the trachea or bronchi, or evidence of marked widening of the carina provide useful information concerning the nature and extent of the lesion, operability, and surgical management.

Cytologic examination of the sputum or bronchial secretions is another valuable diagnostic procedure and one which, with increasing experience, may prove to be the most useful of all diagnostic methods It would seem to have particular value in cases in which the tumor is beyond the range of bronchoscopic visualization. Although this diagnostic procedure was proposed as early as 1877, by Hampeln, it received little serious consideration for almost a half a century In 1935, Dudgeon and Wrigley directed attention to its practical usefulness Even after their report, interest in the method lagged until Papanicolaou published his studies emphasizing the diagnostic value of the smear test for malignant neoplasms with a free surface Much impetus was given this method of diagnosis by these studies, and numerous observers have since directed attention to its practical value in the diagnosis of carcinoma of the lung. Thus, Herbut and Clerf reported positive results in 82 4 per cent of 57 cases of bronchiogenic carcinoma, in their last 27 cases positive results were obtained in 92 5 per cent They believe that examination of bronchoscopically removed secretions is superior to

examination of the sputum, and in addition the former method provides a means of localizing the source of the malignant cells. Positive results of sputum examination were reported by Papanicolaou in 88 per cent of 25 proved cases of carcinoma of the lung. Woolner and McDonald, in a recent report of their analysis of 200 cases in which a diagnosis of carcinoma was made by this means, found that a final diagnosis of lung cancer was established in 190 (95 per cent), and that of the remaining 10 cases, 4 proved to be cancer of the esophagus, larynx or trachea, 4 proved to be falsely positive, and 2 remained undetermined. There can be no doubt from recent reports in the literature that the method is proving increasingly successful and deserves wider application.

Although the demonstration of tumor cells in aspirated pleural fluid is of diagnostic value, the method has greater prognostic than diagnostic significance. While it may establish the diagnosis, it usually indicates a hopeless prognosis.

Aspiration biopsy has also been suggested as a diagnostic method, but in our opinion it should be limited to patients with bronchiogenic carcinoma in whom operative intervention is definitely contraindicated. Although the procedure may provide a positive diagnosis, it is undesirable because of the danger of implantation of tumor cells in the tissues traversed by the biopsy needle. This is not merely a rare possibility. We have observed 3 patients in whom implants have occurred along the site of the aspirating needle, a cure being precluded because of the implanted carcinoma on the thoracic parietes. This complication has also been reported by others.

In a certain proportion of cases a positive diagnosis cannot be established except by exploratory operation. A positive diagnosis was established prior to surgical exploration in 117 (60 per cent) of our 195 cases of resection, and in 208 (67.8 per cent) of the entire series of 307 cases in which exploration was done. Thus, in approximately a third of our cases, exploratory thoracotomy was done in the absence of a positively established diagnosis. This is not greatly different from the experience recently reported by Johnson, Clagett, and Good who found that in their operative series of 123 cases of bronchiogenic carcinoma, the diagnosis was established by exploratory thoracotomy in 60 (48 per cent). On the basis of our experience we are convinced that in cases in which there is good suggestive evidence of pulmonary cancer but in which the diagnosis cannot be established preoperatively despite thorough studies, exploratory operation is justified. Exploratory thoracotomy is a procedure which now carries a minimum risk, and if it is not applied in properly selected cases many patients with carcinoma of the lung will be denied the opportunity for cure. Obviously exploratory thoracotomy should be employed under these circumstances only in properly selected cases for, as emphasized by Churchill, it is important "to determine whether the only chance offered by surgical treatment is in truth a reasonable chance, or whether the cancer is surgically 'out of bounds' beyond any reasonable doubt."

TREATMENT

The only curative treatment for carcinoma of the lung is surgical extirpation of the tumor-bearing lung and regional lymph nodes. Ideally, the procedure should be performed before the lesion has extended beyond the confines of the

lung It is now generally agreed that irradiation therapy is of little or no value in the effective control of the disease and should be used only as a palliative procedure to alleviate symptoms in inoperable cases Similarly nitrogen mustard, methyl-bis (beta-chloroethyl) amine hydrochloride, has been reported to be of possible value in alleviating symptoms in inoperable cases. Our experience with this agent in inoperable cases of carcinoma of the lung, as well as that of others, suggests that the course of the disease is not significantly altered but that in perhaps half the cases temporary alleviation of symptoms is obtained.

With increasing experience we have come to believe that there are relatively few contraindications to exploration As we have broadened the criteria of operability, or more accurately, restricted the contraindications, we have increased the proportion of resectable cases Involvement of the phrenic or recurrent laryngeal nerves is not considered by itself a definite contraindication, for such involvement was present in several of our patients in whom resection proved possible. At present our indications of definite inoperability are the demonstration of distant metastasis, obvious involvement of the trachea or carina, and the presence of malignant cells in the aspirated pleural fluid. In the absence of these findings it is our practice to consider operation, because exploration frequently reveals that a lesion which clinically appears to be inoperable is actually resectable. A similar opinion has been recently expressed by Gibbon

Our experience has also led us to believe that the proportion of resectable cases may be further increased by the use, in addition to resection of the lung, of certain supplemental procedures in cases in which the growth has extended beyond the substance of the lung These procedures include resection of a portion of the pericardium or heart with intrapericardial ligation of the hilar vessels and suture of the auricle, and resection of a part of the diaphragm or thoracic wall In such cases the resection must be considered palliative, for these supplemental procedures must be applied only for extensive growths that have extended beyond the borders of the lung. Our justification for performing such palliative resections whenever the risk entailed is not excessive has the following basis: (1) The remainder of the patient's life is more comfortable when involved, necrotic, and infected pulmonary tissue is removed, because he is spared the sepsis and continued exudation which he would otherwise be obliged to endure. The procedure, therefore, seems warranted from the humanitarian standpoint alone. (2) There is some evidence, as will be shown later, that palliative resection influences favorably the period of survival In fact some of these patients have survived five years with no evidence of recurrence.

Like patients with other forms of cancer, patients with carcinoma of the lung are frequently not in the best condition to withstand an extensive surgical procedure. To a varying extent they may show evidence of loss of weight, protein and vitamin deficiency, secondary anemia, associated pulmonary infection and cardiovascular disturbances For these reasons their preoperative management is of considerable importance, and, in so far as possible, these factors should be controlled or corrected in order to reduce the risk of operation Associated pulmonary infection may be satisfactorily controlled with penicillin although in some instances the use of combined chemotherapy with penicillin, sulfadiazine and streptomycin may be desirable. Because of the associated infection and

nutritional depletion, these patients often have vitamin deficiency, particularly of vitamin C; preoperative vitamin therapy is, therefore, usually indicated. Of particular importance in the preoperative care of these patients is the restoration of hemoglobin and protein deficiency. Because of their chronic debilitating illness these patients often show pronounced reduction of total blood volume and serum proteins with significant degrees of anemia. Our experience has led us to believe that these deficiencies are best corrected, in so far as preparation for operation is concerned, by the ample use of whole blood transfusions. The average amount of blood required for this purpose in our series of cases was 1500 cc. As might be expected in patients in the age group in which lung cancer is most frequent, cardiovascular disturbances are not uncommon. As will be indicated later, our experience has shown that these disturbances may contribute significantly to the operative mortality For this reason we were prompted to include a cardiologist in our thoracic team in order better to control these disturbances both preoperatively and postoperatively.

Technical Considerations

In our experience, closed intratracheal anesthesia with cyclopropane for induction followed by ether-oxygen has proved generally satisfactory. Ample amounts of whole blood, at least 1500 cc., should be available in the operating room. Venoclyses should be started at the beginning of the operation in two separate veins using large bore needles or trocars, for it is sometimes desirable to administer blood rapidly during the operation.

We are still of the opinion, as expressed in previous publications, that pneumonectomy is the procedure of choice because it permits more thorough extirpation of the involved tissue and the possibly involved hilar nodes. Simple lobectomy is reserved as a palliative procedure and for the occasional patient in whom pneumonectomy cannot be tolerated.

Both the anterior and the posterolateral approaches are employed by us, the former being preferred in certain elderly patients with diminished cardiovascular reserve because it has seemed to us that this position is better tolerated. The posterolateral approach is used if the diagnosis is in doubt and a lobectomy may be indicated, if there is evidence of dense adhesions, or if there is peripheral extension of a posterior or lateral lesion. In the anterior approach, as proposed by Reinhoff, the patient is placed in the supine position with the operative side slightly elevated by placing sandbags beneath the shoulder and hip of the affected side, and the arm on this side is supported anteriorly over the face. A lateral cutaneous incision is made over the third intercostal space, extending from the midportion of the sternum to the midaxillary line. The pectoral muscles are divided and the intercostal muscles and pleura are incised close to the upper border of the fourth rib. The third and fourth costal cartilages are divided subchondrally at their sternal junction The internal mammary vessels are then divided between ligatures of crochet cotton (Number 20) or heavy silk. The thoracic wound may then be opened by separating the third and fourth ribs with a rib spreader. In some cases we prefer a slight modification of this anterior approach by entering the thorax through the bed of the subperiosteally resected third rib and its adjoining costal cartilage. In the

the patient is placed in the lateral decubitus position. The classical posterolateral incision is employed, beginning about the level of the fourth interspace posteriorly midway between the scapula and the vertebrae, and extending downward and anteriorly to curve around the tip of the scapula to or just beyond the anterior axillary line. The incision is deepened through the muscular structures overlying the ribs and the pleural cavity entered through the bed of the subperiosteally resected fifth or sixth ribs depending upon the position of the lesion in the lung.

After the pleural cavity has been opened, the lung is mobilized by division of any adhesions which may be present by sharp dissection, and resectability of the lesion determined. A longitudinal incision is then made in the mediastinal pleura immediately posterior to the phrenic nerve and extended above and below around the hilum A flap of mediastinal pleura is thus formed, which is *elevated to expose the mediastinal and hilar structures. Care is taken in mobilizing* this flap to avoid injury to the phrenic nerve and pericardiophrenic vessels. The individual hilar vessels, beginning with the pulmonary artery, are isolated by careful blunt dissection with small pledgets of cotton or gauze on the end of forceps and with the index finger Each of these vessels is doubly ligated and doubly transfixed with heavy cotton (Number 20) or with heavy silk. The two transfixation ligatures lie between the two plain ligatures, and the vessels are divided between the two transfixation ligatures. It is desirable to secure a relatively long length of the pulmonary vessels and for this purpose a special technic of "walking the ligature" has been used This consists of placing the thumb and forefinger around the vessel distal to the ligature and then milking the ligature medially as far as possible by "creeping" or "walking" with the thumb and forefinger The operator holds his fingers in this position as the ligature is tied by the assistant In some instances where, because of encroachment of the tumor, it is not possible to secure an adequate length of the vessel to permit the application of quadruple ligation, a clamp is substituted for the two distal ligatures on the pulmonary side of the vessel and the vessel is divided immediately adjacent and proximal to the clamp so that a relatively long portion of the vessel remains on the proximal stump After the pulmonary artery and the superior and inferior pulmonary veins have been secured and divided in this manner, the bronchus is freed and isolated close to the carina and divided between clamps The lung is removed after division of the posterior reflection of the pleura. A series of end-on interrupted cotton or silk sutures is used to close the bronchus, care being taken to assure complete sealing of the cut ends After thorough dissection and extirpation of all available mediastinal lymph nodes, careful pleuralization of the mediastinum is highly desirable. Whenever possible, the edges of the divided mediastinal pleura are approximated to cover the stumps of the ligated vessels and bronchus If there is an insufficient amount of pleura to cover the hilar stump satisfactorily, a free pleural graft or a pleural flap from the pericardium or from the lower part of the mediastinum may be used. The thoracic wound is then closed without drainage by approximation of the layers with interrupted cotton or silk sutures

Immediately following the operation every effort is made to remove retained secretions from the remaining tracheobronchial tree, bronchoscopy being per-

formed for this purpose if necessary. Oxygen is usually administered by means of a nasal catheter during the first 24 hours postoperatively. Until the patient has completely recovered from the anesthetic, he is kept in the supine position; then he is placed on a back rest. Coughing and active movement are encouraged early. Intravenous fluids and blood are administered as required. Usually by the second or third day the patient is permitted out of bed and generally leaves the hospital between the seventh and tenth days.

MORTALITY

During the past 16 years since the first successful pneumonectomy for cancer of the lung was performed by Evarts Graham, there has been a steady reduction in the operative mortality. This is demonstrated by our own experience. For example, during the first five-year period, 1936 to 1940 inclusive, the hospital death rate following resection was 51.5 per cent, whereas during the last year (1948) it was only 15 per cent. It may reasonably be assumed that this progressive reduction is a reflection of improvements in surgical technic, in anesthesia, and in preoperative and postoperative care.

Although the present operative mortality still seems relatively high, an analysis of the causes of death leaves some doubt that it can be materially reduced without restricting the criteria of operation. Among the 45 deaths (23 per cent) in our resected series of 195 cases, 20 were caused by cardiovascular disturbances, 13 by respiratory infections, 7 by hemorrhage, and 5 by miscellaneous complications such as peritonitis, septicemia, pneumothorax, and anesthesia. These latter causes are chiefly due to technical errors and are, therefore, preventable. Those resulting from infection may also be considerably reduced with more effective chemotherapy. But among the recent cases these causes account for only a small part of the mortality while the major cause of death following operation is a consequence of cardiovascular disturbances. These disturbances are frequently present, together with other constitutional diseases, in many patients in the age group in which pulmonary malignancy is most common. They represent an unavoidable element of risk which must be assumed in the surgical treatment of this condition unless the criteria of operability are so strictly limited that patients in whom this complication is liable to occur are excluded from surgical treatment and are thus denied their only chance of life While this might permit a reduction in the postoperative mortality of the disease, it would not reduce but rather tend to increase the final mortality of the disease. As already indicated, a cardiologist was added to our thoracic team in the hope that with greater care in the preparation of these patients for operation the risk of cardiovascular deaths could be reduced

Another factor which tends to increase the operative mortality is the effort to extend resectability to cases with extensive growths This is shown by our experience with palliative and curative resections. In our most recent analysis of 195 cases of resection the procedure was considered palliative in 138 (70.8 per cent) and curative in 57 (29 2 per cent), the former being determined by extension of the lesion beyond the borders of the lung either grossly or by histologic demonstration of regional lymph node metastasis, and the latter by the

the patient is placed in the lateral decubitus position. The classical posterolateral incision is employed, beginning about the level of the fourth interspace posteriorly midway between the scapula and the vertebrae, and extending downward and anteriorly to curve around the tip of the scapula to or just beyond the anterior axillary line. The incision is deepened through the muscular structures overlying the ribs and the pleural cavity entered through the bed of the subperiosteally resected fifth or sixth ribs depending upon the position of the lesion in the lung.

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Immediately following the operation every effort is made to remove retained secretions from the remaining tracheobronchial tree, bronchoscopy being per-

Analysis of the data to determine whether the progressive improvement through increasing experience, which has taken place in operability and mortality might be reflected in the survival rates revealed no significant differences before and after 1942. This suggests that although improvements in technical management have resulted in a reduction of the hospital mortality they have exerted

TABLE I

INCIDENCE OF OPERABILITY AND RESECTABILITY IN PRIMARY CARCINOMA OF THE LUNG

			Cases Explored		Cases Resected	
Authors		*No. of Cases Observed*	*No.*	*Per Cent*	*No*	*Per Cent*
Churchill	1940	156	52	33 3	27	17.3
Burnett	1941	102	34	33.3	12	11.7
Felter	1943	31	6	19 3	0	0
Overholt	1943	165	80	48 5	41	24 8
Claggett and Brindley	1944	493	90	18 2	45	9 1
Adams	1946	157	94	59.8	49	31.2
Carnes et al	1946	107	21	19 6	12	11.2
Edwards	1946	1,016	173	17 0	70	6.8
Reinhoff	1947		327		112	
Jones	1947	196	66	33 6	39	19 9
Humphreys	1947	125	42	33 6	29	23 2
Sellors et al	1947		246		130	
Brantigan	1948	63	37	58.7	20	31.7
Gagnon	1948	224	86	38 4	49	21 9
Wenzl	1948	120	36	30 0	10	8 3
Lambert	1948	349	70	20 0	25	7.3
Norris	1948	269			30	
Levitt	1948	100	18	18 0	11	11.0
Lindskog and Bloomer	1948	200	72	36 0	33	16 5
Gibbon et al	1948	56	31	53 5	21	37.5
Graham	1948	434	251	57.8	101	23 3
Brock	1948	666	125	18.8	75	11 1
Camblos et al	1949	115	42	36.5	19	16 5
Total*		4,875	1,426†	29 7	688	14 1
Authors' series		548	307	56 0	195	35 6

* The figures shown for Rienhoff, Sellors et al, and Norris are not included in the total

† This figure may actually be somewhat higher for it does not include a small proportion of cases in which operation was refused

little influence on the survival rate, and that other factors such as the nature and extent of the growth are of greater importance in this connection.

The most significant factor affecting the prognosis is the status of the growth; i e, whether or not the lesion has extended beyond the borders of the lung at the time of operation This is clearly shown by a comparison of the survival rates between patients with palliative and curative resections, the former being those in which the lesion had extended beyond the borders of the lung and the latter being those in which the lesion was still confined to the lung Whereas the five-year survival rate for palliative resections was 12.5 per cent, the comparable rate for patients with no extrapulmonary extension of the growth at the time of operation was increased almost fourfold (Fig. 23). The fact, too, that even among patients with palliative resections there was a five-year survival rate of somewhat over 10 per cent is particularly significant, for it lends support

absence of these criteria. Incidentally the fact that in 7 out of 10 cases in which resection was possible the lesion was recognized as being beyond the likelihood of surgical cure emphasizes the need for earlier diagnosis The potentially greater operative risk in palliative than in curative resections is shown by the fact that their corresponding operative mortalities were 25 3 per cent and 17.5 per cent Of interest in this connection and as further evidence of improved management of poor risk patients is the fact that the operative mortality among these palliative resections has been significantly reduced in recent years, the actual figures being 61 2 per cent prior to 1942 and 20 per cent since that date.

An analysis of our experience with primary pulmonary malignancy based upon a series of 548 cases, which has been recently presented, shows that there are a number of factors influencing the prognosis and survival. Among the most important of these are early recognition and proper treatment, the nature and extent of the growth, the degree of malignancy, and the sex and age of the patient.

Of the 548 patients with primary pulmonary malignancy, 194 (35 4 per cent) had inoperable lesions, 47 (6 per cent) refused operation, and 307 (56.1 per cent) had exploration Of the 307 explorations, the lesion was found to be resectable in 195—35 6 per cent of the total series. In brief, this means that of every 3 patients with carcinoma of the lung, one had an obviously inoperable lesion, one had a lesion found to be inoperable at exploration (or refused operation), and one had a resectable lesion. Although these incidences are somewhat higher than those found in a collected series of 4,875 (29 7 per cent for exploration and 14 1 per cent for resection), they are in accord with those appearing in the more recent reports which reflect an encouraging trend toward higher incidences (Table I). This is particularly well illustrated by Björk's analysis of 996 cases of bronchiogenic carcinoma treated at the Brompton Hospital for Diseases of the Chest and at the Royal Cancer Hospital (Free) in London from 1937 to 1946 For the entire series exploration was carried out in 152 (15 3 per cent) and resection done in 75 (7 5 per cent). During the period covered by this study, however, there was an almost threefold increase in the resectability rate, the actual figures being 5 1 per cent in 1937 and 13 5 per cent in 1944. While these figures, as well as those indicated above, suggest a progressive improvement in operability, they are still much too low and emphasize the need for wider recognition of the problem and for earlier diagnosis.

Follow-up studies were made on every patient in our series in whom resection was done and the survival rate over a five-year period has been calculated from these data. The results of this analysis show that a little more than half (52.9 per cent) of the patients in whom resection was performed survive the first six months, somewhat more than a third (36 3 per cent) the first year, and almost a fourth (23 9 per cent) live five years or longer (Fig. 22) Thus, it may be observed that the distribution curve for the survival rate after resection drops rather rapidly within the first year after resection for carcinoma of the lung, but by the second year it begins to be stabilized and continues almost as a plateau from the third to the fifth year. The assumption, therefore, seems warranted that a patient who lives through the second year after operation has a good chance of being alive at the end of five years.

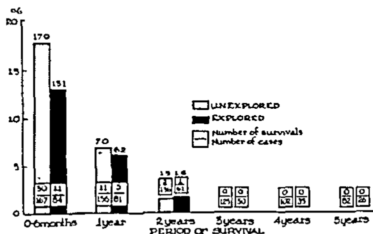


FIG 24 – Gross survival rate in nonresected cases of carcinoma of the lung.

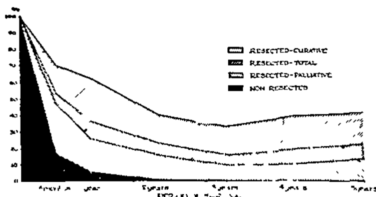


FIG 25 – Graphic representation of survival rates in cases of resection and nonresection for carcinoma of the lung.

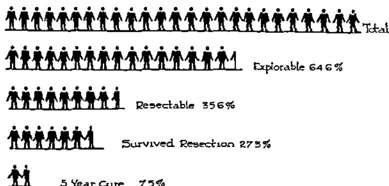


FIG. 26 – Schematic representation of actual survival expectancy in primary pulmonary malignancy, based on the authors' experience.

to our conviction that efforts to perform these resections are justified both for symptomatic relief and prolongation of life

A comparison of these survival rate figures for the resectable cases with those obtained from the nonresectable cases provides further basis of the value of

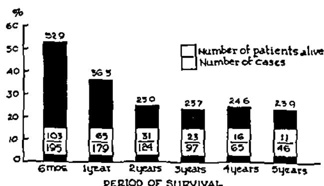


FIG 22 – Gross survival rate after resection in the authors' series of 212 cases of primary pulmonary malignancy.

surgical treatment in carcinoma of the lung. The cases in which resection was not done were divided into two categories—those in which there was no surgical treatment at all because the patient refused operation or the growths were inoperable, and those in which exploration showed the growth to be nonresectable. The respective survival rates of these two groups, however, were practically the

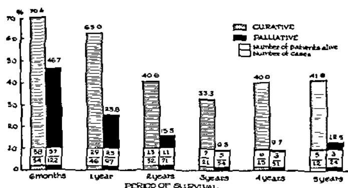


FIG. 23 – Comparative survival rates of curative and palliative resections in the authors' series of 190 cases of primary carcinoma of the lung.

same, with over 95 per cent of the patients dying within the first year and none surviving three years (Fig. 24). A graphic comparison of the results in these cases with those in which resection was possible both for localized and nonlocalized growths makes clear these differences in survival rates and some of the factors affecting them (Fig. 25).

On the basis of our present experience the gross survival rate in carcinoma of the lung at the end of five years is 7 5 per cent (Fig. 26). While this is not an encouragingly high figure, it is as high or higher than the corresponding figure for carcinoma of the stomach, which according to our experience as well as that reported by others does not exceed 6 to 8 per cent at the highest and in some

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series is as low as 2 to 4 per cent It should be recalled, however, that the relative frequency and the general clinical as well as the surgical importance of gastric cancer have been realized for a longer time than lung cancer. This may be reflected by a comparison of their operability and resectability rates. Thus among relatively recent reports in a collected series of 20,235 cases of carcinoma of the stomach exploration was done in 12,120 (59.9 per cent) and resection in 5,439 (26 9 per cent). It may be observed from Table I that in a comparable collected series these corresponding figures are 29.7 per cent and 14 1 per cent, and for our series, 56 0 per cent and 35 6 per cent. Yet the five-year survival rate in carcinoma of the lung is as good as, if not better, than that for carcinoma of the stomach. These observations would seem to justify the opinion expressed previously that: (1) the rate of cure in carcinoma of the lung is now as good, if not better, than that in carcinoma of the stomach, in spite of the fact that there has been a greater general awareness of the latter, (2) with greater appreciation by the profession of the problem of carcinoma of the lung and a consequent increase in the proportion of cases diagnosed early, there should be further improvement in the results of surgical management.

Other factors that may conceivably affect the survival rate are age, sex, and histologic types and grade of malignancy. Using fatality rates, i.e., the number of deaths per patient year of observation, to determine the influence of age upon survival it was found, as might be expected, that fatality rises with increasing age. It was also observed that the greatest increase in fatality which occurred after the age of 60 was caused principally by early postoperative death, which fact supports the clinical impression that the hazards of operation are greater with increasing age.

The predominance of the male sex in carcinoma of the lung and the curious fact that in men epidermoid carcinoma occurs more than two and one-half times more frequently than adenocarcinoma, whereas in women this ratio is completely reversed, suggest that the sex factor is significant in this form of malignancy. This is further supported by the fact that a comparison of the survival rates following resection in the two sexes revealed a consistently more favorable prognosis for women than men over a five-year period.

The significance of histologic type and grade of tumor in prognosis is demonstrated by a comparison of their respective survival and fatality rates Thus the most favorable survival rate was found in patients with epidermoid carcinoma and the poorest in those with undifferentiated carcinoma, while in those with adenocarcinomas it was intermediate. Among both the epidermoid and adenocarcinomas there was a progressive rise in fatality rates from Grades I and II to Grade IV. Among the undifferentiated carcinomas, the small cell and oat cell tumors carried the lowest fatality and the large round and clear cell tumors the highest, with the miscellaneous group intermediate.

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Pancreatitis

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THE PANCREAS WARRANTS special consideration by the physician for several reasons. Its anatomic location deep within the abdomen secludes it from clinical examination. The pathologic states which affect the pancreas are distinguished by mysterious onset, vehement development, and grave consequences. As a source of powerful digestive enzymes, the pancreas is the seat of peculiar biochemical and physiologic processes. Finally, the pancreas produces a vital internal secretion, the hormone insulin, which regulates carbohydrate metabolism.

The word "pancreas" is derived from the Greek words "pan," meaning "all" and "kreas" meaning "flesh" and thus is literally translated "all flesh." The term *indicates that the organ is uniform in composition and consistency*, and contains no bone or cartilage

The clinical management of acute pancreatitis poses a problem that is an integral part of the larger problem of abdominal surgery. Because of the intimate association of the pancreas with neighboring organs, inflammatory disease of the pancreas frequently disturbs the proper functioning of surrounding structures. The clinical diagnosis of pancreatitis is not always easily made, and pancreatic inflammation is often mistaken for other clinical entities of the upper abdomen A review of the literature reveals that much scientific factual knowledge concerning pancreatitis is lacking and that there is dispute about many phases of the disease The present concepts of the physiology and the pathology of the pancreas do not allow physicians in general and surgeons in particular to approach with diagnostic certainty the treatment of inflammatory diseases of this organ. The purpose of this monograph is to discuss some of the problems involved in the understanding and treatment of pancreatitis.

EMBRYOLOGY

The pancreas arises from two distinct primordia; both are entodermal, one from the duodenum, and one from the common bile duct The common bile duct primordium, sometimes bilobular, is the ventral pancreas, when it is bilobular, the left member usually atrophies. The duodenal primordium which arises immediately proximal to the junction between the intestine and the common bile duct becomes the dorsal pancreas. The ventral pancreas together with the common bile duct rotates around the duodenum to the right and posteriorly, describing an arc of 270°. In its definitive position to the left of the duodenum and just below the duodenal primordium, the ventral pancreas fuses along its

the other. The islands of Langerhans do not have an excretory duct system, and therefore their product is termed an internal secretion or hormone, in this instance insulin. The islands vary in size from only a few cells or even a single one to many cells with an aggregate diameter of approximately 3 mm. The islet cells are arranged in cords with numerous intervening capillaries. Normally the islands lie between the acini (interacinar) in the parenchymal stroma of the

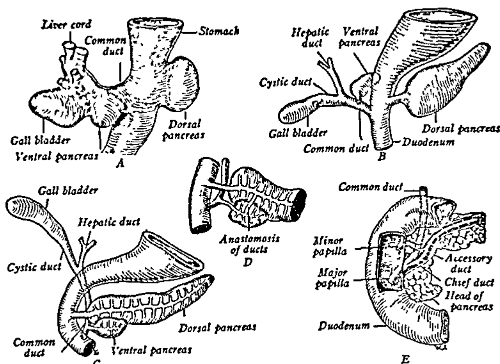


FIG 1 —The various stages of embryologic development of the pancreas and its duct system. (Arey, L B *Developmental Anatomy*, W. B. Saunders Company, 1946)

lobules, but some may be located in the connective tissue between the lobules (interlobular).

ANATOMY

The pancreas, "the abdominal salivary gland," lies molded across the spinal column, its head on the right is enclosed in the loop of the duodenum, and its tail on the left is in contact with the spleen. It varies between a light straw color and a red, according to the amount of blood within the organ It weighs from 30 to 150 gm or more, and its specific gravity is about 1.045 The length *in situ* is approximately 15 cm It consists of an enlarged descending part on the right, the head, and a long body which extends transversely from right to left; the body may be divided into neck, body, and tail for descriptive purposes. When the organ is removed from the cadaver and straightened, it resembles a revolver in shape, if the body be considered as the barrel The shape of the gland, however, is so much influenced by the surrounding parts that its true form is seen only in its undisturbed position, or after hardening *in situ* before removal.

The head is a rounded but irregular disk lying closely against the first, second,

distal border with the mid-portion of the dorsal pancreas The fusion gradually progresses toward the duodenum, involving coincidentally a fusion of the ducts of the two primordia Meanwhile, the duct of the dorsal pancreas (duct of Santorini) becomes constricted or even stenosed, and remains as the accessory pancreatic duct. The duct of Wirsung, the chief pancreatic duct, is in its proximal or duodenal third derived from the duct of the ventral pancreas and empties together with the common bile duct into the duodenum at the papilla of Vater. The ventral pancreas of the embryo forms the greater part of the head of the mature pancreas. The dorsal pancreas becomes the remainder of the head, the body, and the tail The distal two-thirds of the duct of Wirsung is derived from the duct of the dorsal pancreas By the invasion of surrounding mesenchymal connective tissue the primitive entodermal pancreas is divided and subdivided into numerous lobules of glandular tissue, some lobules are larger than others, but functionally they are similar

Because the duodenal end of the duct of Santorini usually becomes constricted, the secretion from that portion of the head drained by the duct of Santorini empties into the duct of Wirsung where the two major ducts join, about a third of the way from the ampulla of Vater. Occasionally there is no communication between the duct of Santorini and the duct of Wirsung, Opie found no communication in 10 of 100 necropsy specimens Naturally, in such an instance, the duct of Santorini must drain into the duodenum. If the outlet of the duct of Wirsung is obstructed, if the outlet of the duct of Santorini is patent, and if there is communication between the two systems, the secretion from the whole gland may drain into the duodenum via the duct of Santorini. Opie believed that the duct of Santorini might have served as an outlet for the whole gland in about half of his 100 cases In a small percentage of human cases (6 per cent, according to Opie), the duct of the ventral pancreas fails to develop as a major structure, and, therefore, the main pancreatic duct enters the duodenum at the papilla of the duct of Santorini In pigs, sheep, oxen, and ruminants generally, the duct of the dorsal primordium (Santorini) serves as the chief duct. The various stages in the development of the pancreas are illustrated in Fig. 1.

The primordia are originally simple tubes of entoderm which branch extensively, and by the time the dorsal and the ventral pancreas have fused, each consists of an intricate duct system The innumerable terminals, or intercalary ducts, differentiate into tubular secretory acini which liberate the pancreatic juice. The acinar or zymogenous parenchyma constitutes the exocrine portion of the pancreas

The endocrine portion, similarly derived from entodermal tubes, consists of numerous (500,000 to 1,500,000) extensively vascularized aggregations of smaller polygonal cells, the islands of Langerhans. They contain three morphologic types of granular cells, A, B, and D, as described by Bloom. The islands begin to appear during the third month of fetal life. After they have differentiated from the distal ends of the terminal intercalary ducts, the islands either develop from these ducts independently, or they lose connection by obliteration of the original lumen of the connecting ducts. Though both acinar and islet cells derive from the intercalary ducts, the cells, once differentiated, cannot reconvert one into

The borders between the surfaces call for no special description. Both inferior borders are notched by the superior mesenteric artery, and the superior border by the celiac axis as well. The anatomy of the pancreas is illustrated in Fig. 2.

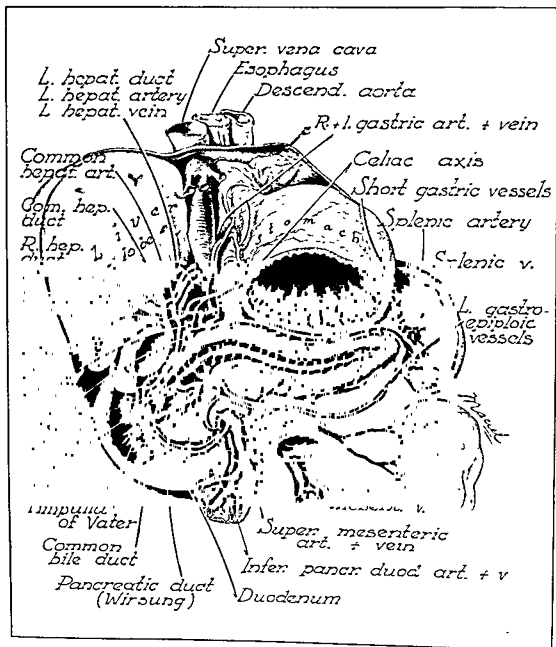


FIG. 2 —Anatomy of the pancreas, showing its regional relationships

The pancreas has no well defined capsule, but is surrounded by a thin fibrous sheath which is continuous with the interlobular connective tissue The chief excretory canal in the adult is the duct of Wirsung, which, beginning in the tail, runs in the center of the body toward the right. When the duct of Wirsung reaches the head, it bends downward, then turns to the right as it approaches the duodenum Branches originate from the main duct at right angles and

and third parts of the duodenum It overlaps both the second and third parts ventrally and tends to insinuate itself dorsally to the duodenum. It may occasionally overlap the fourth part. The shape of the head of the pancreas varies with the form of the encircling duodenum The diameter of the head from above downward is rarely less than 7 cm and may be greater. Its separation from the neck is anatomically indicated by a groove on the front of the gland which contains the gastroduodenal branch of the hepatic artery. The head rests posteriorly on the inferior vena cava, sometimes on the right renal vein, and may approach the right suprarenal body. The head is at the level of the first and second lumbar vertebrae and often part of the third.

The body, including the neck and tail, is triangular in shape with three surfaces, (1) posterosuperior, (2) anterosuperior, and (3) inferior. Because of its tortuous course the body seems shorter than it is. Starting to the right of the spine at the level of the first lumbar vertebra, it crosses the spine transversely to the left and dorsally and then extends as far as the spleen, where it curves ventrally The end of the body, the tail, may continue across the spleen, in any event the tip turns downward toward the pelvis.

The neck, 2 to 3 cm. in length, crosses the portal vein with a forward convexity, and is deeply grooved on its dorsal surface by that vein. The tail is variable in form If it lies in front of the spleen, the tail is more or less pointed, but if it ends against the gastric surface of that organ, it may have a true terminal concave surface conforming accurately to the space it occupies.

SURFACES

(1) The posterosuperior surface is deeply grooved by the portal vein, which may be entirely surrounded by glandular tissue. To the left of the portal vein the posterosuperior surface faces first the inferior vena cava, then the segment of the aorta between the celiac axis above and the superior mesenteric artery below The next portion lies consecutively on the left pillar of the diaphragm, the left suprarenal capsule, and the left kidney. If the tail is long, it may rest on the gastric surface of the spleen. The splenic artery and vein form horizontal grooves on the posterior surface. The lower, containing the vein, is the longer and deeper, and extends from the tail of the pancreas to the portal vein, inclining toward the lower border of the gland as it approaches its termination The upper groove contains the splenic artery as it progresses from its origin at the celiac axis to the tail of the pancreas

(2) The anterosuperior surface, the largest of the three, slants downward and forward, presenting a concavity which forms a part of the stomach bed This surface measures 4 cm in breadth but may exceed 5 cm On the lower margin of this surface, opposite the aorta, a swelling, the omental tuberosity, is often found. This lies behind the lesser curvature of the stomach at the lower end of the vertical part of this curvature.

(3) The inferior surface, the smallest, rarely as much as 2 cm. in breadth, rests on the lower layer of the transverse mesocolon The inferior surface is rounded and irregular, except for a smooth concave portion above the duodenojejunal junction To the right of Treitz's ligament the surface is grooved by the superior mesenteric artery

the course of the arteries. They are all tributaries of the portal system, and some open directly into the portal vein. The pancreas is drained by an extensive network of lymphatic vessels which lead to the splenic and celiac lymph nodes. A small group of lymph nodes lies above and ventral to the head of the pancreas.

The nerve supply of the pancreas consists of nonmedullated fibers from both the parasympathetic and sympathetic systems. The vagus and splanchnic nerves send these fibers to the pancreas by way of the celiac, splenic, and superior mesenteric plexuses.

HISTOLOGY

Histologically the pancreas is composed of: (1) the acinar cells and the associated excretory duct system, (2) the islands of Langerhans, and (3) the interlobular connective tissue

The secretory parenchyma of the pancreas is embryologically derived from the ductal epithelium. For descriptive purposes the structure of the parenchyma is best understood after consideration of the duct system. The ends of the finest branches of the tree-like excretory duct system are surrounded by the acinar cells of the secretory parenchyma. The lumen of the main pancreatic duct is lined with a single layer of columnar epithelium, in which an occasional goblet cell is lodged. Small mucous glands empty into the large ducts, the walls of which are formed of dense collagenous tissue containing a few elastic fibers. In the smaller ducts the columnar epithelium decreases in height. When the ducts enter the lobules of acinar tissue, the mucosal lining changes to flat epithelial plates, and the ducts connect directly with the acini. The terminal epithelium of the intercalary ducts protrudes into the acinus as the centro-acinous cells, which are spindle-shaped and may be surrounded by the secretory cells of the acinus

The acini of the pancreas assume a tubular form. The acinar cells appear blunted and pyramidal in shape, and rest on a well defined membrana propria. The blunted cellular tips point inward to form the central lumen of the acinus. The cytoplasm exhibits two well differentiated zones: an inner one, next to the lumen, which contains many fine granules (zymogen or secretory granules), and an outer zone, next to the basement membrane, which is homogeneous and free from granules. The relative breadth of these two zones varies with the functional activity of the cells During fasting, the secretory granules increase in number, and the granular zone widens to infringe on the clear basal zone. When pancreatic secretion flows during digestion, the granular zone diminishes. In the pancreas which has been "exhausted" by continuous secretion, only occasional secretory granules are seen in the acinar cells. A period of rest restores the granular zone to normal proportions.

The nucleus of the acinar cell is spherical or ovoid and rests in the basal zone of the cytoplasm Occasionally a small round structure termed the paranucleus is seen in the cytoplasm close to the nucleus. The paranucleus may be concerned with the production of zymogen granules. Between the acinar cells canaliculi that empty into the lumen of the acinus occur, but do not reach the basement membrane. Intracellular secretion vacuoles may be demonstrated at times by Golgi stains but cannot be regarded as constant details of the cell.

receive bundles of smaller ramifications. The diameter of the duct near its end is about 5 mm. It descends to the wall of the duodenum ventral to the common bile duct The two structures usually enter the duodenal wall separately, but they join in a common ampulla, the ampulla of Vater, where their secretions mingle before being discharged into the duodenum The term *papilla of Vater* refers to the elevated area in the duodenal mucosa, caused by the presence of the *ampulla of Vater*

The duct of Santorini maintains a vestigial, and in some instances, functional outlet into the duodenum at a point about 3 cm. above and ventral to the papilla of Vater. The orifice may be difficult to locate in the duodenal mucosa but can often be identified by a small raised ring The left end of the duct of Santorini joins the main duct at the point where the duct of Wirsung curves downward into the head of the pancreas. Since the duct of Santorini ordinarily decreases in size as it approaches the duodenum, the flow of secretion within that duct is presumably directed away from the duodenum and toward the duct of Wirsung In the presence of a patent duodenal outlet for the duct of Santorini the normal direction of flow may be reversed under three circumstances: (1) if no communication exists between the duct of Santorini and the duct of Wirsung, (2) if the duodenal portion of the duct of Wirsung is congenitally stenosed or atrophic, (3) if the outlet of the duct of Wirsung is artificially obstructed by agents such as tumor or stone.

The relation of the pancreas to the peritoneum is significant The ventral pancreas was embryologically suspended in the ventral mesentery of the primitive gut, while the dorsal pancreas lay free in the dorsal mesentery. The embryologic rotation of the duodenum to the right placed that structure against the posterior abdominal wall where it lost its mesentery and became a retroperitoneal organ By the same process the pancreas was bound posteriorly to the retroperitoneal tissues, and consequently its posterior surface is not covered with peritoneum except at the tip of the tail The pancreas lies at the base of the transverse mesocolon between the leaves of peritoneum which cover its anterosuperior and inferior surfaces. Because the position of the pancreas between the greater and lesser peritoneal cavities at their separation by the transverse mesocolon is such that its broad anterosuperior surface faces the lesser cavity, while the narrow inferior surface presents toward the greater cavity, the major portion of the pancreas lies in the base of the lesser peritoneal cavity

The arterial blood supply of the pancreas is abundant, and originates from the splenic, hepatic, and superior mesenteric arteries The splenic artery supplies the greater part of the body and the tail The hepatic artery provides the head of the pancreas with small branches, but it nourishes the head to a greater extent through the gastroduodenal artery and its branch the superior pancreaticoduodenal artery The superior pancreaticoduodenal artery follows the inner curve of the duodenum downward along the ventral aspect of the pancreas The inferior pancreaticoduodenal artery, after arising from the superior mesenteric artery, runs to the right and upward between the third portion of the duodenum and the pancreas, until it anastomoses with the superior pancreaticoduodenal artery. Occasionally a similar anastomosis between the two pancreaticoduodenal arteries occurs on the dorsal surface of the head. The veins follow

of Wirsung in dogs. He recognized the three main ferments we know today, protein-splitting, starch-splitting, and fat-splitting, and his attempt to form a permanent fistula between the main pancreatic duct and the abdominal skin suggested methods for the study of pancreatic secretion under relatively normal conditions.

Heidenhain and co-workers in Breslau during the 1870's were especially interested in all phases of pancreatic physiology, and among the many reports from his laboratory are those concerning the histologic mechanism of cellular secretion, the measurements of secretory pressure, and a method of creating a permanent pancreatic fistula which was almost identical to that used by Pavlov.

Of all the investigators in this field Pavlov springs first to mind. The results of a vast number of experiments, performed in his laboratory during the last three decades of the 19th century, clearly defined the role of pancreatic juice in intestinal digestion Pavlov elucidated the importance of the vagus nerve in controlling and stimulating secretion, and he emphasized the extreme sensitivity of the pancreas to various stimuli, such as anesthesia, operative manipulation, emotional upset, or agents producing vasoconstriction within the gland, all of which result in ready inhibition of the secretory process. Pavlov, as well as all subsequent investigators, found that, in order to study the pancreas under conditions of relatively normal function, he was faced with the problem of developing a satisfactory and comparatively permanent source of pancreatic juice in the living, normal animal. He accomplished this by creating an operative fistula between the main pancreatic duct and the abdominal skin; this fistula, when healed, would produce pancreatic juice over a period of days or weeks. This technic, first described in 1879, involved excising a circular portion of the duodenal wall and mucosa with the papilla of the main pancreatic duct at its center, and transplanting the duodenal mucosa and duct orifice onto the skin surface of the abdominal wall Although simple in theory, the operation invites many complications, such as infection, scarring of the fistula, or retraction of the delicate duct from intra-abdominal tension. Even when the investigator succeeds in creating a functioning, well healed fistula, he is burdened with grave physiologic difficulties because of the continuous loss of large quantities of pancreatic juice, which irritates the abdominal wall and drains the subject of electrolytes, fluids, and digestive ferments. Nevertheless, Pavlov's pancreatic fistula has been and still is widely used for the collection and study of pancreatic juice under varying conditions and in response to various stimuli.

Bayliss and Starling, English physiologists, added the next important chapter to the story of pancreatic digestive function when in 1901 they described the formation of secretin Secretin, formed in the duodenum and carried by the blood to the pancreas where it excites digestive secretion, provided the first recorded instance of hormone action in the body and thus indirectly set the stage for the general understanding of the endocrine glands.

Clinicians and physiologists during the 19th century were aware of a connection between pancreatic disease and diabetes, but no concrete knowledge was available until von Mering and Minkowski in 1889 succeeded in completely removing the pancreas of dogs and producing a consequent diabetes. Discovery of this remarkable fact stimulated much work. Although most investigators

The islands of Langerhans appear as small collections of cells, 0.3 mm. in diameter, which lie between the tubular acini. These cell areas are constant features of the pancreas in man and other mammals, as well as in birds, reptiles, and amphibians. Their distribution within the pancreas varies. Opie has shown that they are almost twice as numerous in the tail as in the remainder of the gland. The islands are enclosed by a delicate envelope of connective tissue. The islet cells, despite a common origin with the acinar cells, differ markedly. The islet cells are small, pale, polygonal rather than pyramidal in form, and show no granules when stained with hematoxylin and eosin. Special stains, however, reveal intracellular granules that differ from the zymogen granules in the acinar cells The islet cells are arranged as a network consisting of solid cords or trabeculae, the meshes of which are occupied by blood capillaries of large size, the whole recalls the arrangement of hepatic tissue. Extension of the system of excretory ducts has not been demonstrated to enter islands of Langerhans. The secretion of the islet cells must enter the blood stream through the extensive capillary bed which is present.

The interlobular connective tissue of the pancreas surrounds the lobules of glandular tissue and supports numerous blood vessels, nerves, and ducts Fat cells are prominent features in the interlobular stroma. The acinar and islet cells have a stroma of their own, which consists of a network of fine reticular fibrils The interlobular fibrous tissue does not normally extend into the lobules.

PHYSIOLOGY

The pancreas serves the body in two important ways, first, in aiding the digestion of assimilated foodstuffs within the intestine by the production of pancreatic juice, second, by regulating carbohydrate metabolism in the body by the formation of insulin within the islands of Langerhans. Thus, the general concept of pancreatic function is a simple one, but it is important to state that a great deal remains to be known both about pancreatic ferments and about insulin, and it is entirely possible that the pancreas regulates human physiology in important ways not yet known For the present the subject can be discussed briefly by describing the function of external pancreatic secretion (the digestive secretion which reaches the duodenum by the pancreatic ducts) and by mentioning the role of internal pancreatic secretion (the hormone insulin, which passes directly from the islands of Langerhans into the blood stream to be conveyed to distant parts of the body). Because the physiology of diabetes is a complicated and unsettled subject, we shall not attempt to review it systematically, inasmuch as it is not essential to an understanding of the problem of pancreatitis Because diabetes may secondarily appear in chronic pancreatitis when the organ is severely damaged, we cannot ignore it altogether

Historical

The growth of knowledge about the pancreas drew its initial impetus from the work of physiologists rather than from clinical observation Claude Bernard presented the first detailed reports on pancreatic physiology in 1849, when he described the properties of pancreatic juice obtained by cannulating the duct

in a fasting dog to about 18 cc. per hour, or 240 to 450 cc. during 24 hours. Babkin, who has worked on the physiology of digestive glands for many years, has stated that, when the dog's pancreas is protected from the influence of secretin by diverting all gastric and biliary juice from the duodenum, the pancreatic secretion is much lower, varying between 1 and 2 cc. per hour.

Secretion of pancreatic juice in man is likewise continuous. Information on this score has come from clinical sources, which can give only suggestive and not exact figures. Individuals may develop pancreatic fistulas following operation on or near the pancreas, and the pancreatic juice which is lost onto the skin can be collected and studied. Although such individuals cannot be considered to have a completely normal pancreas, and although the observer has no way of knowing in these individuals how much pancreatic juice still enters the intestine normally by the duct system, the information so gathered has definite value, inasmuch as persons with pancreatic fistulas frequently drain secretion for several months, during which period they may be in relatively good health except for the presence of the fistula. Many authors have reported on this matter, giving figures for daily pancreatic secretion during normal feeding that vary widely (from 30 to 1770 cc.) with an average of 400 to 600 cc. Miller and Wiper (1944) reported the highest daily volume yet recorded, 1770 cc., in a 26-year-old soldier who developed a pancreatic fistula 13 days following an emergency laparotomy for a perforating gunshot wound of the epigastrium. Their observations, as well as those of others, support the belief of physiologists that pancreatic secretion in humans is continuous.

The pancreatic secretion in a normal person can be collected and examined for presumptive daily volume and other characteristics by inserting a tube into the duodenum via the mouth and by aspirating the fasting contents of the duodenum, when the flow of bile is at a minimum. Another tube, opening into the stomach, is attached to a suction apparatus in an attempt to prevent gastric juice from entering the duodenum Despite these precautions, the juice collected from the duodenum only approximates total pancreatic secretion, since there is invariably some contamination with bile and gastric secretion. Agren and Lagerlof (1936) reported by this method an average of 36 cc. of fasting secretion per hour or 864 cc. for 24 hours.

Pancreatic Enzymes

The protein fraction of pancreatic juice is by far the most important since it contains the digestive enzymes These can be grouped in three classes: the proteolytic enzymes which digest protein, the amylolytic enzymes which digest starch and its components, and the lipolytic enzymes which digest fat. External pancreatic secretion, in contrast to gastric juice or bile, has the ability to digest all three classes of food stuffs.

Proteolytic Enzymes. (1) Trypsin is the chief ferment. First described by Kuhne in 1867, it was finally isolated chemically by Northrop and Kunitz in 1932 Trypsin works most efficiently in an alkaline medium corresponding to the normal pH of pancreatic secretion, and is a more powerful ferment than gastric pepsin It acts on native, unaltered protein or on peptones and proteoses, which are the end products of peptic digestion of protein in the stomach. It breaks

believed that the islands of Langerhans were intimately connected with the pathologic physiology of diabetes, two major obstacles prevented a prompt solution of the problem In the first place, if an insufficiency of normal islet tissue was the cause of diabetes, then logically the administration of pancreatic extract should correct the deficiency and correct the diabetes; yet all attempts in this line were unsuccessful for over 30 years following von Mering and Minkowski's experiments, until Banting and Best in 1921 succeeded in preparing an extract of pancreatic tissue that did correct the deficiency of islet cell activity in diabetes. Secondly, pathologists were quick to note in the 1890's, as well as later (Warren, 1938), that, although one would expect pathologic changes in the islands of Langerhans in all cases of diabetes, such were found at best in only 50 per cent of the cases studied. From an anatomic standpoint, therefore, it was difficult for physicians to agree that diabetes was caused only by a derangement of islet cells. This difficulty still confronts us today, but may well be resolved by recent researches, which indicate that structures other than the pancreas, especially the pituitary, thyroid, and adrenal glands, play important roles in the causation of diabetes.

DIGESTIVE FUNCTIONS OF THE PANCREAS

General Characteristics of External Pancreatic Secretion

The contribution of the pancreas to alimentary digestion consists of a clear, watery secretion, the pancreatic juice, which flows into the duodenum from the duct of Wirsung The secretion is colorless and slightly mucoid, resembling saliva. Water comprises about 98 per cent of the juice, the rest being protein and organic matter The specific gravity of juice from a fistula has varied from 1 005 to as high as 1 019, depending on a fluctuation in solid content, which changes according to the nature of the secretory stimulus. A more detailed explanation of this change will be given later. The juice is always alkaline, but varies from pH 7.10, slightly acid to the body, to pH 8 65, strongly alkaline. The variation in pH is controlled to some extent by the type of secretory stimulus, but from a chemical standpoint the pH is dependent on the relative proportion in the juice between the two negative ions, chloride and bicarbonate, the sum of which balances the positive sodium ions. When the proportion of bicarbonate ions is high with respect to the chloride, the pH rises and vice versa The solid content of the juice, averaging a little less than 2 per cent by weight, is about one quarter protein and the rest organic compounds. Miller and Wiper (1944) reported a case with a pancreatic fistula which secreted juice containing 190 to 340 mg per cent of total protein. Thus, their patient with a maximum recorded daily secretion (1770 cc.) and a maximum protein concentration (340 mg per cent) would lose about 6 gm of protein a day in the secretion. This loss, though small, is continuous, and therefore is important to the poorly nourished patient.

The total daily volume of secretion is not accurately known, but physiologists in the past have estimated it at about 700 cc a day. Formerly it was thought that pancreatic juice flowed only during periods of digestion, but observations on dogs with pancreatic fistulas suggest that secretion is continuous and amounts

juice. Cowgill, in Howell's *Textbook of Physiology*, lists the following enzymes as occurring in pancreatic secretion or in the pancreas itself, carboxypeptidase, aminopeptidase, erepsin, nuclease, guanase, adenase. Others, still unidentified, are also undoubtedly present.

Amylolytic Enzymes. (1) Amylase (diastase, amylopsin): This starch-splitting enzyme is similar to the amylase that occurs widely throughout the biologic kingdom. According to Sumner and Somers, it can be found in practically all plants, animals, and micro-organisms. Within the human, amylase also occurs in the saliva (there called ptyalin), in leukocytes, in blood plasma, and in urine. It hydrolyzes native starches at an optimum pH of 7, producing maltose, a disaccharide. The final breakdown into monosaccharides takes place further along in the small intestine. The amylase, normally found in human blood serum and urine, can be readily demonstrated by laboratory tests. This enzyme is increased in amount during acute inflammation of the pancreas. Although the *mechanism of this increase is not understood, it is commonly presumed that the* damaged secretory cells allow the escape of an abnormal amount of the digestive enzymes into the blood stream. However, the supply of amylase in the blood probably comes in part from sources other than the pancreas, since after total pancreatectomy the enzyme is still present in blood samples (Fallis and Szilagyi). Dozzi believed that there is good evidence to suggest that blood amylase is partly formed in the liver. Liver damage may cause a fall in blood amylase.

(2) Maltase. A small amount of this enzyme can be found in pancreatic secretion. It hydrolyzes maltose into glucose, thus producing a trace of glucose during pancreatic digestion of starch.

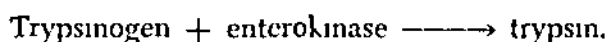
Lipolytic Enzymes (Esterases). Pancreatic Lipase (Steapsin): Like the other pancreatic ferments this one works best at an alkaline pH (optimum pH 8) but is also active in faintly acid juices. It is easily destroyed by strong acid solutions and by trypsin. Like amylase, it can be detected in blood serum of normal individuals; also like amylase, it tends to rise in acute inflammation of the pancreas.

This lipase is a powerful fat-splitting enzyme, overshadowing gastric lipase in importance. It bears the burden of fat digestion. It changes insoluble neutral fats into fatty acids and glycerol, substances which the intestinal epithelium can absorb. A second characteristic of lipase is its ability to emulsify liquid fats. For instance, if pancreatic juice is added to olive oil, after a number of hours emulsification of the mixture occurs. The process of emulsification follows partial digestion of the oil, and it is initiated by the formation of a soap from the union of a fatty acid with one of the alkaline ions present in pancreatic juice, usually a sodium ion. Once a little soap has been made, the rest of the neutral fat is easily emulsified. Emulsification of fat is highly important to its digestion, since finely dispersed fat particles offer a much greater surface on which the water-borne enzymes can work.

Pancreatic lipase, however, normally works in close co-operation with bile. The combination of the two juices digests fat four to five times faster than pancreatic juice alone. The bile salts appear to be the agents responsible for this increased efficiency by exerting their influence in three ways: (1) they enhance the activity of lipase, possibly in the rôle of a coferment, (2) they are excellent

down large molecules to the last step before the release of the basic amino acids, the polypeptide and peptide stage

Trypsin is, strangely enough, inactive in pure pancreatic juice collected directly from the pancreatic duct. A pupil of Pavlov, Shepovalnikov, showed how the body activates this powerful enzyme. By adding a small amount of duodenal juice to the pancreatic juice, he noted that the trypsin immediately gained full power. He called the activating substance that is present in duodenal mucosa as well as in duodenal juice *enterokinase*. Because of this distinction from the active form, inactive trypsin has been given a special name, trypsinogen Trypsinogen, then, is the form in which the ferment is secreted by the acinar cells and carried to the duodenum within the ducts As soon as the pancreatic juice enters the duodenum, the sequence of events takes place in the following manner



Trypsinogen + enterokinase ——→ trypsin.

Other agents may also activate trypsinogen, as observation of a pancreatic fistula reveals. When inactive pancreatic juice remains in contact with normal skin, excoriation develops within several days. Tissue juices, pus, raw surfaces speedily activate the tryptic power of the pancreatic juice Calcium ions are supposed to activate trypsinogen in concentrations above 0 02 molar, and yet, according to Miller and Wiper, a certain amount of ionizable calcium is normally present in pure fistula secretion (2 20 to 3 24 mg per cent). Trypsin also has the power of activating trypsinogen, so that once a small amount of trypsin is formed, it can change the remaining trypsinogen into a potent form It is interesting to speculate about the fact that the body keeps the proteolytic enzymes *of the pancreas in an inactive, harmless state until they are in actual contact* with the food in the duodenum *Is this mechanism necessary in order to protect the pancreas from autodigestion? What would happen if trypsinogen became activated within the pancreas?* As yet answers to these questions are not known. In 1900 Landsteiner concluded that the albumin fraction of blood plasma contains a substance that protects the living cells of the body against tryptic activity. According to Northrop and Kunitz, this antitryptic substance is also present in the pancreas, thus perhaps affording the organ protection against its own secretion It may be that all living cells have such a protective device. In all events, trypsin disappears in the process of completing its work in the duodenum and small intestine, and only minute traces can be found in the lower ileum.

(2) Chymotrypsin This proteolytic enzyme closely resembles trypsin, differing in that chymotrypsin specifically curdles and digests milk in a manner similar to that of gastric rennin. In pure pancreatic juice it likewise exists in an inactive form, chymotrypsinogen Chymotrypsinogen becomes active only in the presence of trypsin Enterokinase does not cause activation of chymotrypsinogen.

(3) Miscellaneous Proteolytic Enzymes The proteolytic power of pancreatic juice was originally thought to be the work of one enzyme, "trypsin" Actually a variety of enzymes has been discovered in addition to pure trypsin. These enzymes split the intermediate products of protein digestion into simple end products. Individually they are not important for the purpose of this discussion except to emphasize the complexity of the enzymatic properties of pancreatic

obtained in pure crystalline form by Agren. It can be purchased commercially for clinical purposes. It is a protein-like substance of low molecular weight (5,000), resembling polypeptides in nature.

Once secretin has been formed in the duodenal epithelium, it passes into the blood stream and reaches the secretory cells of the pancreas, where without the agency of nerve endings it directly provokes a profuse, watery, alkaline secretion, relatively poor in ferments but rich in inorganic salts. Whereas atropine inhibits pancreatic secretion following vagal stimulation, it has no effect on the flow following administration of secretin (usually given intravenously). Thus secretin is a true hormone which performs its task independently of the nervous system.

The hormonal control of the pancreas is in delicate balance. As soon as the alkaline pancreatic juice enters the duodenum, the hydrochloric acid from the stomach is neutralized, and secretin is no longer formed in the duodenum. If the stomach sends more acid chyme, more secretin is formed until the pancreatic juice again neutralizes and destroys the stimulus.

The difference in the effects produced by vagal stimulation and secretin stimulation is worth emphasizing. As noted above, nervous stimuli bring forth a juice which is rich in ferments but small in volume, whereas hormonal stimuli provoke a profuse secretion, relatively poor in ferments and high in alkalinity. These facts appear to correlate with the normal physiologic sequence of eating. When food is swallowed and collected in the stomach, reflex vagal impulses cause the pancreatic acinar cells to produce the digestive ferments that will be needed shortly. Because the volume of juice is small, very little is lost into the duodenum until the stomach expels its acidified digest into the duodenum. When this happens, secretin begins its task at once by initiating a profuse alkaline juice which washes the ferments from the ducts into the duodenum. The two types of stimuli are complementary and work together to achieve a most efficient result. Some British workers (Harper and Raper) believe that in addition to the effects of secretin and the vagus nerve there is another hormone, called *pancreozymin*, which, although similar to secretin, like the vagus, excites, a rich flow of enzymes. Its presence, however, does not detract from the importance of vagal stimuli in the secretory process.

Another interesting way of differentiating the effects of hormonal from nervous stimuli is to examine the pancreas histologically. Heidenhain, over 70 years ago, noted that the zymogen granules in the acinar cells decreased after the animal had been fed, and he presumed that these granules represented precursors of important elements in pancreatic juice. It is now known that vagal stimulation of the pancreas will also diminish the number of granules, whereas administration of secretin hardly changes it at all. Therefore the granules probably represent products which are secreted as digestive enzymes.

Secretogogues. This group of pancreatic stimulants includes a diversity of agents, among which are protein derivatives such as peptones and proteoses, acids, fats and fatty acids, soaps, and even water. When introduced into the duodenum, they excite pancreatic secretion. The mechanism of their effect is not entirely clear, but it appears that they work independently of secretin. The vagus nerve seems to be stimulated by the presence of fat and peptone in the duodenum. The secretogogues produce a secretion rich in enzymes and when the vagus is

emulsifiers of fat, thus permitting more efficient digestion of fat in the aqueous suspension of the duodenum, (3) they form water-soluble complexes with fatty acids, which can then be absorbed by the intestinal epithelium. Although pancreatic lipase can split fat without the help of bile, the process is greatly speeded when both are working together.

Control of Pancreatic Secretion

The pancreas in its capacity as a producer of digestive ferments puts forth juice in response to the intake of food. It has already been stated that external pancreatic secretion flows continuously in small amounts, but over and above this basic flow the quantity and quality of secretion change to meet the additional work of digesting a meal. This adaptive mechanism has intrigued physiologists, and a great many experiments have been done to elucidate its nature. In general, there are three classes of stimuli to which the external secretion reacts. (1) nervous stimulation, especially from the vagus, (2) hormonal stimulation, notably from secretin, (3) an ill-defined group of stimulants, called secretogogues, among which are meat extracts. Their mode of action is not always clearly understood.

Nervous Stimulation. In a series of brilliant experiments Pavlov and co-workers established the importance of vagus control over pancreatic juice. He divided the vagus nerve in the neck and exposed it onto the skin surface. After an interval of four days he electrically excited the lower segment leading to the abdominal viscera. A slow flow of thick concentrated juice, especially rich in digestive ferments, followed promptly. The same type of juice can be produced by more normal stimuli which also are probably transmitted in reflex fashion via the vagi. For instance, sham feeding in a dog whose esophagus empties onto the chest instead of into the stomach, will produce thick secretion, high in enzymatic content. The effect of vagal stimulation can be abolished by giving atropine, and this drug has been used in attempts to reduce the loss of secretion in human pancreatic fistulas. Conversely, pilocarpine will stimulate pancreatic flow in a manner similar to vagal stimulation, and pilocarpine is frequently used experimentally as a substitute for electrical stimulation of the vagus nerve. The sympathetic nerves apparently do not exert an important influence over pancreatic secretion, yet ephedrine seems to reduce pancreatic flow through its vasoconstricting powers. It has been used clinically with success on several occasions to lower the amount of pancreatic secretion lost in human fistulas. Doses used have been 0.048 gm. every two hours (Craft). Reflex nervous pathways which do not traverse the central nervous system run between the jejunum and pancreas of the cat and cause inhibition of pancreatic secretion, according to Kuntz and Richins (1949).

Hormonal Stimulation. Pavlov had already established the power of the vagus nerve over the pancreas when in 1901 Bayliss and Starling announced the discovery of a substance, later called *secretin,* which produced a greater flow of pancreatic juice than ever achieved with vagal stimulation. When hydrochloric acid from the stomach runs into the duodenum, it combines or acts upon a substance in the duodenal epithelium to form secretin. This substance can be extracted from duodenal mucosa which has been treated with hydrochloric acid, and it has been

DEPRESSION OR ABSENCE OF EXTERNAL PANCREATIC SECRETION

Despite its undisputed importance in the process of digestion, pancreatic juice probably is not essential to life. Deprivation of pancreatic juice in humans may occur in conditions which cause total obstruction to the outlet of the pancreatic ducts, such as tumor of the head of the pancreas, sclerosis from chronic pancreatitis, pancreatic lithiasis or, most clearly, following total pancreatectomy. As surgeons become more skillful in their technics, this operation is becoming more frequent It usually is performed for carcinoma of the pancreas and occasionally to relieve the pain of diffuse calcification of the pancreas.

The important factors in pancreatic juice, as already noted, are the three types of digestive enzymes, the proteolytic, the amylolytic and the lipolytic; finally, there is the possibility of an essential lipotropic factor, which because of its controversial nature will be disregarded for the moment It is worth knowing what effects can be expected in the absence or in marked depression of the digestive enzymes.

ABSENCE OF PROTEOLYTIC ENZYMES

Despite the presence of pepsin in the stomach and erepsin in the small bowel, protein foods do not usually digest well when pancreatic juice is absent. In instances of markedly poor protein digestion one may see grossly undigested meat fibers in the stool or find microscopically striated muscle fibers. This condition is often called creatorrhea (azotorrhea) Aside from the gross and microscopic appearance of the stool, the presence of extra undigested food usually causes the stool to be bulkier in size than normal and often may cause a mild diarrhea. The amount of unabsorbed protein can be more accurately determined by measuring the nitrogen content Normally 1 to 3 gm. of nitrogen are lost in the daily feces. During creatorrhea the value may rise to 6 gm or more a day. The presence of such large amounts of unabsorbed nitrogen in the stool is practically diagnostic of diminished or absent pancreatic secretion

The presence of undigested meat in the stool has been recognized as a symptom of chronic pancreatic disease since the middle of the nineteenth century, but unfortunately it is not a specific finding that is always present. For some reason, *individual intestinal tracts vary in their ability to digest and* absorb protein in the absence of pancreatic juice. Some individuals have maintained good digestion and absorption of protein after pancreatectomy without taking pancreatic substitutes, whereas other individuals with merely diminished pancreatic flow, as in chronic pancreatitis, may develop marked creatorrhea. This same variability has been seen experimentally in dogs whose pancreatic juice has been excluded from the duodenum. In practice, however, as emphasized by Pratt, who believes that in the complete absence of pancreatic juice there is always some decrease in protein absorption in the intestine, it is wise to give pancreatic extract to all patients who show evidence of impaired pancreatic secretion. This treatment will improve the efficiency of digestion and allow patients to gain weight. The dosage of pancreatic extract as reported in the literature varies greatly, but between 4 to 15 gm daily in divided doses of pancreatin has been efficient. Although the effective amount varies with each patient, about 10 gm daily is usually sufficient. According to Dragstedt, a standard preparation of pancreatic extract also contains a sufficient amount of the hormone lipocaic to be active in the body.

paralyzed their effect is for the most part lost. Babkin (1944) gives a summary with references of the work done on this somewhat confusing problem. In all events, these secretogogues provide another form of stimulus of broad scope for the production of pancreatic juice Their action may be especially important in those instances when the gastric chyme is not acid, as in gastric anacidity.

THE PANCREAS AND FATTY INFILTRATION OF THE LIVER

While studying diabetes in depancreatized dogs, workers in MacLeod's laboratory in Toronto noticed that even though the animals were adequately treated with insulin, they almost invariably developed massive enlargement of the liver from infiltration with fat Following pancreatectomy the liver increases three to four times normal weight, and the per cent of total fat content may rise to 12 times normal This change is not fatal, according to Chaikoff and Entenman, who have maintained 3 depancreatized dogs for more than four years without feeding them any pancreatic substitute, though the animals fall off in weight and show abnormally low concentrations of blood lipids.

This fatty change in the liver of dogs can be prevented by feeding them raw pancreas The question then arises as to what element in the pancreas prevents the liver damage Since insulin obviously has no effect, a substance elaborated by the acinar cells has been presumed to be the active agent One group of workers, headed by Dragstedt, has extracted a substance from the glandular tissue of the pancreas, which they call *lipocaic*. It is considered to be a true hormone, an internal secretion of the pancreas which, given orally or parenterally, will prevent fatty change in livers of depancreatized dogs Another group of investigators, led by Montgomery, has extracted from the pancreas a substance which, although different from lipocaic, also protects the livers of depancreatized dogs. As opposed to lipocaic, it is excreted in the pancreatic juice into the duodenum, and, therefore, Montgomery considers it a product of external pancreatic secretion. Both of the lipotropic factors are claimed to be efficient in preventing the fatty change in the liver Substances which so regulate metabolism of fat that excess lipids are not deposited in the liver are frequently termed *lipotropic* factors

Another simpler substance, choline, will easily prevent fatty changes in the liver of depancreatized dogs if given in larger amounts than normally present in the ordinary kennel diet (that is, in doses of 30 mg per kilogram per day) *Although neither of the two extracted fractions mentioned above exerts its action* by virtue of containing choline, it is equally efficient if given in sufficient amounts, and is considerably easier to obtain

The problem of the lipotropic factor in the pancreas is still highly controversial and must be decided on the basis of further experimental work, but the clinician can no longer entirely ignore it if surgeons continue to do total pancreatectomies One of the human cases reported by Fallis and Szilagyi survived 14 months after pancreatectomy, during which interval the patient received no choline and only sporadic doses of pancreatic extract Because at necropsy the liver showed no invasion of fat, they concluded that with a normal diet a supplementary lipotropic factor is probably unnecessary for the depancreatized patient. To another patient they administered choline chloride in doses of 1.3 gm three times a day.

follows exclusion of pancreatic juice from the duodenum, there may be sites of aberrant pancreatic tissue within the gastro-intestinal tract which still produce some pancreatic juice.

Loss of Pancreatic Juice by External Fistula

In addition to replacing the lost pancreatic enzymes with pancreatic extracts one must realize that the patient with an external pancreatic fistula is losing large quantities of fluid daily, and that even more disastrous to his economy is the daily loss of sodium and chloride ions. The blood chemistry in such a case will reveal diminished values for both sodium and chloride ions. The depleted sodium reserves in the body mean loss of extracellular fluid and marked dehydration. One must not be misled by a normal or only slightly diminished carbon dioxide combining power, which does not mean that the body has a normal amount of alkali. Gamble has shown that in pancreatic fistula, as in high obstruction of the gastro-intestinal tract with vomiting, the loss of chloride as well as sodium causes the blood carbon dioxide combining power to be maintained at near relatively normal levels, in order that the sum of bicarbonate plus chloride may equal the total value for sodium One can thus visualize that even with a diminished amount of sodium ions, with a corresponding decrease in chloride ions the carbon dioxide combining power might be normal. Figure 3 represents graphically, after the manner of Gamble, the alterations in the various constituents in the acid-base structure of the blood plasma after a period of continuous loss of pancreatic juice through an external fistula. In all events, the parenteral administration of saline in amounts slightly greater than the volume of juice lost by the fistula will restore the electrolyte pattern to normal and correct dehydration. Any excess chloride ion so given will be eliminated in the urine. The relatively healthy patient with a fistula who loses only a small amount of pancreatic juice daily will naturally be able to make good his deficit by an added oral intake of salt and water But loss of weight and dehydration in a patient with an external pancreatic fistula should arouse suspicion of a sodium deficiency, and until this has been corrected recovery cannot be expected Dehydration in a patient with a pancreatic fistula may also be misleading in that the blood of such a patient may reveal normal counts for hemoglobin and red cells, whereas actually, because of diminished blood volume from dehydration, the patient is markedly anemic. Once dehydration has been corrected, the blood should be rechecked for the presence of anemia and hypoproteinemia. Both of these conditions are frequently present in such patients because of prolonged malnutrition and frequent anorexia.

Carbohydrate-regulating Mechanism of the Pancreas

No attempt will be made to discuss fully the physiology of diabetes. For a a brief and readable account the reader can consult Best and Taylor: *The Physiological Basis of Medical Practice.* Destruction of pancreatic parenchyma by disease usually involves the islands of Langerhans as well as acinar tissue, and diabetes may complicate any type of pancreatic ailment, although, in general, diabetes is surprisingly infrequent following pancreatic damage. Shumacker (1940) says that 3 to 10 per cent of patients surviving acute pancreatitis develop diabetes. For this reason one must be concerned, when considering the function of the

ABSENCE OF LIPOLYTIC ENZYMES

Pancreatic lipase is the most important fat-splitting enzyme of the gastrointestinal tract, and when it is absent, the stool usually shows an abnormal amount of unabsorbed fat, a condition called steatorrhea In such instances, the stool is bulky and greasy, and oil droplets may be seen on its surface. The color is usually light because bile pigments have been masked by the abnormal constituents. A foul odor characteristically arises from rancid breakdown products of the unabsorbed fats and fatty acids Typically, diarrhea and excess gas formation are present because of the increased bulk of the stool and because of the abnormal products of incomplete digestion Microscopically, many oil droplets can be seen after staining a smear of feces with a fat stain, such as Sudan IV. For additional information one can chemically analyze a 24-hour stool specimen, a laborious task. Whereas total fat content of normal feces averages 18 per cent of the dry weight, in steatorrhea it may reach 60 to 70 per cent. An index of the efficiency of fat digestion supposedly can be found in the proportion of unsplit fat (neutral fat) to digested fat (fatty acids). Normally from 20 to 60 per cent of the fat of the stool is undigested (neutral fat), and for some unknown reason lack of pancreatic lipase does not alter that relationship. As in the case of protein digestion and absorption in the absence of pancreatic juice, there is great variation from individual to individual in the efficiency of assimilation of fat under similar circumstances Some show slight and others marked impairment, as evidenced by gross steatorrhea. One must remember that steatorrhea also occurs in tropical sprue, and the treatment of that syndrome differs from that of the case of insufficient pancreatic juice (pancreatic insufficiency). In sprue or in idiopathic steatorrhea the nitrogen content of the stool is relatively normal, whereas in pancreatic insufficiency the nitrogen content of the stool is greatly elevated The steatorrhea of pancreatic insufficiency will, like creatorrhea, respond to the oral intake of pancreatic extract in doses already discussed One prominent benefit of pancreatic extract, which cannot be completely accounted for, comes from its occasionally dramatic ability to relieve the profound anorexia which may afflict patients following pancreatectomy. If either steatorrhea or creatorrhea is present, the other condition will frequently, but not always, be found

ABSENCE OF AMYLOLYTIC ENZYMES

The digestion and absorption of carbohydrates is about as efficient in the absence of pancreatic amylase as in its presence; hence, no particular step need be taken toward replacing it when it is lacking Pratt believed that in such a case carbohydrate absorption is impaired, but that bacterial fermentation of the unabsorbed portion prevents it from being found in the feces.

In a general discussion of the importance of external pancreatic secretion, Brunschwig (1947), who has had wide experience with resections of part or the whole of the pancreas for carcinoma, has recently stated: "The problem of prolonged survival in adequate nutrition without external pancreatic secretion is not as yet fully elucidated Following resection of the head of the pancreas and the duodenum one of three situations may obtain. (1) there may be normal stools, (2) stools may be bulky, pale, foul, pasty, but not abnormally frequent; (3) there may be frank steatorrhea." He further suggested that where no alteration in stool

islands. The next most common lesion, sclerosis or fibrosis of the islands, occurred in 20 per cent of his cases. From the gross or microscopic anatomic examination of a pancreas, therefore, one cannot be certain whether or not it came from the body of a diabetic patient.

One may pose a converse situation. What pancreatic lesion invariably leads to diabetes? The answer is, none except for total destruction or extirpation of the organ. Fortunately, the supply of islet tissue in the normal pancreas is extremely abundant. This organ, even when severely damaged, can carry on efficiently its function of regulating carbohydrate metabolism. Karsner in his *Textbook of Pathology* has stated that diabetes is found in ". . . fibrosis, fat infiltration, arteriosclerosis, acute pancreatic necrosis, abscess, carcinoma, and others . . . but destruction of the organ must be extensive involving approximately seven-eighths of the gland in order to be significant." In his work on the pancreas Opie first stressed the fact that scarring of the pancreas which involved the individual secretory acini (interacinar) is much more likely to produce diabetes than interlobular fibrosis, which does not invade the pancreatic lobules but remains confined to the interlobular tissue. This observation has been confirmed, though many glands with interacinar fibrosis occur without associated diabetes.

It appears fairly clear that diabetes is not dependent alone on the failure of the islands of Langerhans to function. The roles of the pituitary, adrenals, and thyroid have not been fully elucidated, but these glands undoubtedly are implicated in the altered physiology of the disease. An interesting piece of evidence confirming this view is that patients who have had the pancreas surgically removed require only moderate amounts of insulin, 30 to 40 units of protamine a day, which is well below the amount frequently required to control the usual diabetes Furthermore, these patients, even if deprived of insulin for three days, show only a slight tendency to develop ketosis (Dixon et al.; Fallis and Szilagyi).

When pancreatic ducts are obstructed by disease or by ligation, the acinar tissue beyond the point of obstruction becomes atrophied over a period of several months, because its secretion cannot escape. The islands of Langerhans in the affected area usually are not influenced by the destruction of acinar tissue, and they continue in an unaltered state to form insulin and regulate carbohydrate metabolism. Banting made use of this fact in order to prepare his first extract of insulin The survival of the islands serves to emphasize that even in the complete absence of pancreatic juice with marked atrophy of the gland, carbohydrate metabolism may still be perfectly normal

In summary, it is safe to say that the pancreas can sustain much damage without the advent of diabetes, but in all diseases of that organ one must look for the presence of diabetes and be aware that it may develop in the future if there is further involvement of the pancreas. If it does develop, it must be handled and treated as is diabetes in its usual form Once developed, it tends to remain mild or only moderately severe

For more detailed information on the physiology of the pancreas one may consult general texts on physiology, such as Starling's *Principles of Human Physiology*, Howell's *Textbook of Physiology*, Best and Taylor's *Physiological Basis of Medical Practice*. Precise technical data on the digestive enzymes may be found in Sumner and Somers' *Chemistry and Methods of Enzymes*. Babkin's *Secretory Mechanism*

diseased pancreas, with the internal as well as the external secretion of that gland

The islands of Langerhans produce a hormone insulin, which, when it enters the blood stream, is followed by a lowering of blood sugar Since diabetic patients suffer from an inadequate supply of insulin, one might expect to find that such *patients have a reduced number of normal islands of* Langerhans. On the con-

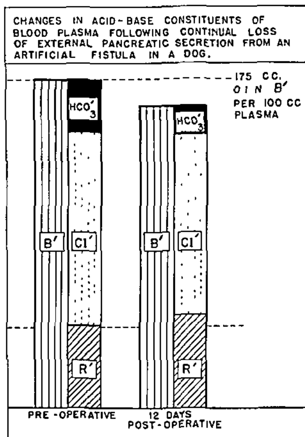


FIG 3 —The columns represent comparative amounts of ionic constituents in the blood plasma The total basic ions are represented by B', the total acidic ions consist of the sum of HCO'$_3$ (bicarbonate ion), Cl' (chloride ion), and R' (organic acid ion)
(Condensation of a table by J L Gamble and M A McIver, 1928)

trary, only about half of the patients with diabetes show histologic evidence of *inadequate islet tissue*

Warren (1938) has recently investigated this problem thoroughly In a survey of 484 pancreases from diabetic patients of all ages he found 26 per cent with completely normal islands of Langerhans He estimated, in absence of an accurate count, that 95 per cent of his cases showed a decreased number of islands, but other authors have reported only 20 per cent with diminished quantity. No particular pathologic lesion in the pancreas accompanies diabetes The most frequent change according to Warren is hyalinization *of the islands*, but this was found *in* only 41 per cent of the 484 cases and, when present, did not involve all of the

the passage of bile into the duodenum and diverts the bile into the duct of Wirsung, but necropsies on cases of acute pancreatitis only occasionally disclose an impacted stone in the ampulla. Spasm of the sphincter of Oddi can without question be associated with the reflux of fluid from the common duct into the duct of Wirsung, as proved by cholangiography. The relation of sphincter spasm to pancreatitis has not been well defined. It is undecided whether the presence of bile in the pancreatic ducts at physiologic pressures is harmful or innocuous. In the majority of postmortem specimens, the terminal orifices of the common bile duct and the duct of Wirsung enter the ampulla of Vater in such a manner that reflux of fluid from one duct to the other is possible when the outlet of the ampulla

TABLE I

A Classification of Possible Etiologic Factors in Acute Pancreatitis

1. Reflux of bile into pancreatic duct resulting from obstruction of ampulla of Vater by:
   a Calculus
   b Spasm of sphincter of Oddi
2 Obstruction of pancreatic ducts by
   a. Pancreatic calculus or ampullary calculus
   b Tumor, inflammation (edema or fibrosis)
   c. *Epithelial metaplasia in small ducts*
   d. Surgical ligature
   e Duodenal diverticulum
3 Infection
4. Vascular factors
5. Trauma
   a. Accidental
   b. Surgical
6. Miscellaneous
   a Reflux of duodenal contents into the pancreatic ducts
   b. Alcoholism
   c. Anaphylaxis

is obstructed. Variations from the normal anatomic structure may prevent communication between the pancreatic and biliary ducts

ii *Obstruction of the pancreatic ducts and autodigestion of the pancreas.* Experimental obstruction of the pancreatic ducts produces fat necrosis and acute edema of the pancreas with subsequent parenchymal atrophy and fibrosis, but acute pancreatitis with hemorrhage and necrosis rarely develops, even though the gland is actively secreting at the time of obstruction Rich and Duff claim that obstruction to the outflow of pancreatic juice by gross lesions, such as tumor and stone, or by the microscopic lesion, metaplasia of the epithelium in the small ducts, ruptures the duct system and allows pancreatic secretion to escape into the parenchyma, where trypsin becomes active and initiates necrosis. The concept of autodigestion of the pancreas assumes that trypsin is activated *within* the gland A mechanism for the activation of trypsin in acute pancreatitis has not as yet been clearly demonstrated Acute obstruction of the pancreatic ducts is followed by a rise in serum amylase, even though acute pancreatitis with hemorrhage and necrosis does not develop

iii *Infection* Experimentally the injection of bacteria into the pancreas does not produce acute pancreatitis. Chronic inflammation of the extrahepatic biliary

of the Digestive Glands is devoted to explaining the physiologic functioning of the digestive process.

ETIOLOGY OF PANCREATITIS

Although the cause of pancreatitis either in its acute or chronic form is not known, numerous attempts have been made to solve the mystery of its etiology both in the laboratory and at the bedside, but nonpartisan observers, even today, generally agree that a wholly satisfactory answer has not yet been given. The difficulty in obtaining that answer may well rest in the fact that workers are individually talking about different phases of pancreatitis without so realizing. Each hypothesis may be true for the small segment of facts that it covers without actually contradicting other theories, which also are only valid for other segments of facts If observers, instead of offering a comprehensive explanation of pancreatitis, would restrict their conclusions to the evidence they have accumulated, we might one day find that the assorted theories, when pieced together into a larger picture, would, like the united parts of a jigsaw puzzle, create a clear intelligible whole

In this light each of the theories and assorted facts bears equal importance until more is known, and while a brief summary may seem confusing and inconclusive, it will emphasize that no one theory in its present stage is adequate to account for all facts The reader will notice that most of the discussion is concerned with acute pancreatitis This is almost inevitable, if one presents work based on experimental data, since acute pancreatitis is a dramatic, abrupt entity, reproducible in the laboratory, whereas chronic pancreatitis is more ill-defined, less well controlled, and, therefore, more resistant to etiologic analysis.

A number of more or less complete reviews of the literature bearing on etiology are available in English Dragstedt, Haymond, and Ellis (1934), Rich and Duff (1936), Jones (1943), Rienhoff and Pickrell (1945) note most of the important ideas and references The discussion that follows does not pretend to be all-inclusive. It will attempt to indicate the significant points and select work illustrating those points, without cataloguing the vast amount of experimental and clinical papers on this subject. Since our ultimate ignorance precludes an accurate description of the early stages of the pathogenesis of this disease, various authors usually tailor a theoretical explanation of pathogenesis to fit the particular etiologic concept in question Therefore, in treating the origin of pancreatitis we shall not draw a sharp line between etiology and pathogenesis, and we shall call on any facts that may help to substantiate or clarify the theory at hand A brief summary of the theories discussed in this monograph follows:

Causes of Pancreatitis

1 *Bile flows into the pancreatic duct because an obstruction at the ampulla of Vater creates a common channel between the common bile duct and the duct of Wirsung.* The experimental injection of bile into the pancreatic duct usually produces acute pancreatitis. The high incidence of cholelithiasis in acute pancreatitis favors the supposition that a gall stone, impacted in the ampulla, blocks

grenous Pancreatitis, and of Disseminated Fat Necrosis." The opening portion of the lecture dealt with the extent of clinical knowledge until that date. To emphasize the importance of Fitz's contribution we shall briefly summarize the significant work prior to 1889.

Classen in 1842, on the basis of 6 collected cases and one of his own, established that acute inflammation of the pancreas could occur, although Fitz believed that none of these cases had been proved to be inflammatory in nature. However, Classen probably did see the disease, since he also described symptoms that fit our present concept of acute pancreatitis, such as deep-seated epigastric pain unrelieved by vomiting, and frequent fainting.

The next important review of pancreatitis was that of Friedreich (1875) whose report, according to Opie, was the first significant one. From anatomic studies in 4 cases, including one of his own, he offered a description of the pathologic process in pancreatitis. Primary acute pancreatitis tended to cause hemorrhage in or about the pancreas and ended in gangrene, in ichorous peripancreatitis, or in suppurative confluent abscesses. Secondary acute pancreatitis consisted of either a "granular degeneration," as found in infectious disease, or circumscribed, metastatic abscesses from a purulent focus elsewhere in the body. Friedreich did not define a precise symptomatology for the disease. Large cysts and abscesses involving the pancreas, sometimes even separating it from its surroundings (sequestration), were considered by Klebs (1876) to have arisen from inflamed lymph nodes in that area This concept grew into what became essentially the bacterial explanation of the origin of pancreatitis. Klebs also suggested that in the absence of inflammation pancreatic hemorrhage might be due to a corrosive action of pancreatic secretion.

Balser in 1882 added the final link to the chain of pathologic lesions in acute pancreatic disease by describing fat necrosis and associating this peculiar nodule with pancreatic inflammation.

We can see that by 1889 all the important factors in the pathologic anatomy of acute pancreatitis had been described. hemorrhage, hemorrhagic necrosis, gangrene, suppuration, abscess, cyst, and fat necrosis, but these clearly called for correlation into a systematic whole with a consistent clinical picture before a rational basis of treatment could be evolved. Reginald Fitz performed this invaluable task for the medical profession On the basis of 70 collected cases of the acute disease, over a dozen of which he had personally observed, he defined a sequence of pathologic events and established a definite clinical picture, for the most part unaltered today. Massive pancreatic hemorrhage, causing death in one-half to 36 hours, was considered to be a special entity, resulting from the rupture of an artery from an unknown cause. Hemorrhagic *pancreatitis with* bloody exudate in the interstitial tissue and with necrotic parenchyma was generally fatal in two to four days; but if the disease was prolonged, gangrenous pancreatitis formed which usually caused death in 10 to 18 days. Both of these forms were frequently accompanied by fat necroses.

Under the category of suppurative pancreatitis, Fitz placed those cases of subacute or chronic nature in which the pancreas was usually the seat of a large abscess, accompanied by progressive emaciation, chills, and upper abdominal swelling. Fetid, pale stools and diabetes (one case) appeared in prolonged cases.

tract commonly accompanies pancreatitis, but specific bacteria are not regularly found in clinical cases of acute pancreatitis. Experimental acute cholecystitis in cats does not cause acute pancreatitis with necrosis The presence of suppuration in the pancreas implies a bacterial infection, either primary or secondary.

iv. *Vascular Factors.* Because of the rich blood supply of the pancreas experimental infarction is not easily produced. The experimental production of embolus or thrombosis in the pancreatic vessels does not cause a spreading hemorrhagic necrosis, similar to that in acute pancreatitis. It has been suggested that vasoconstriction in the pancreatic vessels may initiate ischemic necrosis. Necropsy studies of acute pancreatitis have failed to reveal a consistent primary lesion of the pancreatic blood vessels.

v *Trauma* Acute pancreatitis occasionally follows mechanical injury to the pancreas from contusions and perforating wounds of the upper abdomen or from surgical procedures on or near the organ. After pancreatic injury the serum amylase frequently rises although acute pancreatitis does not develop clinically.

vi. *Miscellaneous* (a) Reflux of duodenal contents into the pancreatic ducts: The passage of duodenal contents into the pancreatic ducts may occur on rare occasions, but it is infrequently associated with acute pancreatitis.

(b) Alcohol Clinical observations indicate that alcoholism is frequently associated with acute pancreatitis An experimental explanation of this association is lacking.

(c) Anaphylaxis The concept of an anaphylactic origin of acute pancreatitis is for the most part still theoretical.

Survey of Early Knowledge About Pancreatitis

During most of the 19th century practicing physicians considered the pancreas somewhat of a medical curiosity The brilliant contribution of Bernard on pancreatic physiology may have stimulated fellow physiologists, but clinicians were apparently sublimely indifferent to the new concepts Even though Claude Bernard produced acute pancreatitis by injecting oil and bile into the pancreatic duct, no one knew enough about diseases of that organ to appreciate what he had done. By the 1880's a few erudite professors in Germany displayed their vast clinical knowledge by citing an occasional rare case of acute inflammation of the pancreas, which they had seen. Senn, a Chicago surgeon, wishing to place the treatment of injuries to the pancreas on a rational basis, in 1886 reported quite a remarkable series of experiments on the dog's pancreas, which he subjected to a variety of injuries, but like his German contemporaries he stated, " . . . acute idiopathic pancreatitis is an exceedingly rare affection, only a few well-authenticated cases of the disease have been reported." Although interest was quickening and the forces were rallying for an attack on pancreatic disease, it was not until 1889, when Fitz sounded the battle cry, that the charge began. Then, within the space of the next 12 years the bulk of our knowledge about pancreatitis and the basis of all our theories regarding its etiology were achieved

Fitz's communication on the subject took the form of a lecture before the New York Pathological Society on February 16, 1889, and is reproduced in complete form in the *Medical Record* of that year, under the title, "Acute Pancreatitis: A Consideration of Pancreatic Hemorrhage, Hemorrhagic, Suppurative, and Gan-

of Körte (1899), Lanceraux (1899), Oser (1898). All 3 authors were aware of a connection between gallbladder disease and pancreatitis and particularly of the role of gallstones in this disease. They believed that gallstones, when lodged in the terminal portion of the common duct, might obstruct the outflow of pancreatic juice and allow bacteria from the inflamed area surrounding the gallstones to penetrate into the pancreatic ducts, where rapid proliferation would occur in the static secretion. They also noted that in the case of pancreatic stone with obstruction a similar mechanism might arise from organisms migrating up the pancreatic duct from the duodenum. The clinical observation of the coincidence of pancreatitis and gallstones has had perhaps more influence on the subsequent interpretation of the disease from an experimental, clinical, and therapeutic view than any other factor, and any serious attempt to explain the lesion must take account of this observation. Opie, it must be remembered, had full benefit of these clinical views. With this introduction we can proceed to a discussion of current theories of the etiology of pancreatitis.

Reflux of Bile into Pancreatic Ducts

The most popular theory about the etiology of acute pancreatitis states that bile, when it flows into the pancreatic ducts, damages the pancreas and initiates acute pancreatic necrosis.

Opie's Common Channel Theory Opie was the first to propound the theory of biliary reflux into the pancreatic ducts when in 1901 he performed a necropsy on a man who had died of acute hemorrhagic and necrotic pancreatitis with fat necrosis. He found a small gallstone obstructing the papilla of Vater, and noted also bile in the duodenal end of the pancreatic duct. Working from this evidence, he brilliantly conceived that bile in this instance had been unnaturally forced into the pancreas, and to test this hypothesis he injected bile into the duct of Wirsung of 6 dogs. He found hemorrhagic pancreatitis and fat necrosis in almost every instance. The proof seemed complete. For the first time an experimental method of producing in a physiologic way hemorrhagic necrosis and fat necrosis practically at will had been found, for bile appeared to be more efficient in this regard than any of the large number of agents hitherto tried He had clinically demonstrated a mechanism whereby bile might be injected into the human pancreas by the inner bodily processes This mechanism consisted of: (1) the formation of a "common channel" between the choledochus and the main pancreatic duct, when the proper outflow of bile was blocked by an obstructing calculus at the papilla of Vater, (2) a propulsive pressure, derived from the contractile power of the gallbladder superimposed upon the secretory pressure of the liver, which forced bile into the pancreas.

Opie's explanation seemed so plausible and well proved that it was soon accepted in all lands and in a modified form has remained to this day the favorite of clinicians Within a few years numerous investigators had satisfied themselves that bile injected into the pancreatic duct could experimentally produce acute pancreatitis, and this fact has been and is generally accepted by those interested in the problem We shall later point out why some authorities believe that these experimental findings in dogs should not be transposed as an explanation of acute pancreatitis in humans.

Strangely enough, fat necrosis was conspicuously infrequent within this group. He believed that the hemorrhagic and gangrenous forms were complications of "a relatively simple affection, viz., gastroduodenitis." In discussing treatment he advised draining lesser omental abscesses, but warned against laparotomy in the early stages of the disease. "It [acute pancreatitis] has been repeatedly confounded with acute intestinal obstruction, and has thus led, in several instances, to an ineffective laparotomy, an operation which, in the early stages of this disease, is extremely hazardous."

Once Fitz had properly classified the pathology of acute pancreatitis, characterized its clinical course and stressed its frequency, then succeeding workers, confident of a secure foundation, could turn their talents toward uncovering its etiology This search began almost immediately and was pursued with great vigor by a number of investigators, first in Europe and later in this country. We shall indicate the lines of this research in general terms. Opie's book provides many references to the authors of this period The first efforts were directed toward the lesion, fat necrosis. R. Langerhans in 1891 showed that fat necrosis could be produced by injecting pancreatic juice into fatty tissue He presumed that lipase rather than bacteria or degenerative processes was responsible for the lesion Flexner (1897) agreed and demonstrated the presence of a fat-splitting enzyme in the fat necroses from human cases.

The next step was to produce fat necrosis or hemorrhagic pancreatitis in the experimental animal. In general, the efforts, none of them wholly successful, involved the following groups of experiments: those using trauma to the gland, such as transection, crushing, ligature; those with ligation of the pancreatic ducts alone or in combination with occlusion of pancreatic blood vessels, those with occlusion of the vascular supply of the gland in order to allow the onset of autodigestion, those with injection of bacteria into the pancreatic ducts or glandular substance, those with injection of irritating chemicals into the pancreatic ducts with or without ligature, and those with injection of duodenal juice or hydrochloric acid in concentrations similar to gastric juice By each of these methods fat necrosis and less frequently hemorrhagic lesions in the pancreas were formed in a certain number of animals It was generally believed that the damage so induced allowed the enzymes in the secretion to escape their natural boundaries and then digest normal tissues The damage supposedly followed from direct extension of these agents to adjacent tissues, although an occasional case of pericardial fat necrosis suggested a blood- or lymph-borne extension Without examining this experimental evidence further at present, we wish to emphasize the extensive and varied nature of the experimental approach to pancreatitis even before 1900. With such a rich background of known facts, Opie was able to direct his thoughts along slightly different lines, and he produced a fruitful source of investigation that still thrives On the basis of an observation at necropsy he injected bile into the pancreatic duct and promptly obtained hemorrhagic necrosis and fat necrosis.

During this period of extensive experimentation clinical knowledge of pancreatic disease increased correspondingly. In addition to a greater experience in acute pancreatitis, the clinician achieved some idea of what to expect in chronic pancreatitis. The extent of this knowledge can be observed in the monographs

Archibald repeated and confirmed Oddi's original observation that hydrochloric acid when placed in the duodenum will cause spasm of the sphincter. In several cats he observed the onset of acute pancreatitis when he injected infected bile into the gallbladder and at the same time induced spasm of the sphincter by the use of hydrochloric acid. He postulated that the contracted muscle acted on the outlet of the common duct in the same way as an impacted calculus and thus created a common channel between the pancreatic and common ducts which would allow biliary reflux and its attendant damage. On the basis of this hypothesis he advised cutting of the sphincter (sphincterotomy) as treatment for patients with recurrent bouts of pancreatitis. Since hydrochloric acid can definitely provoke spasm of the sphincter, he presumed that hyperacidity in the stomach might cause clinical spasm, which, when coupled with infected bile, would prepare the ground for the onset of acute pancreatic necrosis.

Although Archibald's demonstration of sphincter spasm has been repeatedly observed since that time, no one has been able to produce acute pancreatitis in a convincing number of experiments merely by inducing spastic obstruction of the papilla. For instance, Wangensteen and his associates (1931), working with a large number of cats, were unable to obtain reflux of bile or pancreatitis unless they obstructed the papilla mechanically with a ligature.

Inflammatory Obstruction of the Ampulla of Vater. A third and probably infrequent cause of obstruction at the ampulla of Vater follows inflammatory swelling of that structure, as emphasized by Balo and Ballon. The inflammation may be "catarrhal" in type, with marked swelling of the mucous membrane in response to infectious agents Following surgical exploration of the common duct, trauma to the ampulla may induce transient swelling and blockage of that structure. Theoretically, any such edematous obstruction may divert bile into the pancreatic duct.

The Manometrics of Sphincter Spasm. The truest way of determining the presence or absence of sphincteral spasm consists in observing the behavior of fluid pressure within the common duct This may be done by connecting a graduated hollow tube to a catheter in the common duct or, if the cystic duct is patent, in the gallbladder, obviously, the procedure can be carried out only at operation or postoperatively on patients who have had common duct or cholecystic drainage. In evaluating the presence of sphincteral spasm one must consider the possibility of fixed obstruction at the papilla such as occurs in ampullary stone or tumor, or in constriction from a fibrotic pancreatic head. The readings which will be obtained with the biliary manometer may help to differentiate fixed obstruction from spastic obstruction of the papilla Under normal circumstances bile enters the duodenum in periodic spurts under the control of the sphincter. Characteristically, the pressure in the choledochus mounts until it reaches a threshold range, normally 50 to 150 mm of water, under this influence the sphincter relaxes, and bile is expelled into the duodenum The pressure at which the sphincter opens gives some indication of its function. With a "breaking point" above 150 mm. it is considered spastic or hypertonic (Colp and Doubilet), below 50 mm, unduly relaxed or hypotonic Although the breaking point can be measured with a single manometer when the continuous secretion of bile has built up the requisite pressure, most investigators advise the use of a perfusion

Irritant Effect of Bile Salts. The mechanism of the injurious effect of bile on the pancreas is not entirely obvious, and should be better understood. Simon Flexner's work in 1906 on a dozen dogs seems to be the basis for the statement in the literature that the bile salts, sodium glycocholate and sodium taurocholate, are the injurious agents in the bile, whereas the colloidal matter of bile is protective Although this may be true, his conclusions appeared to rest on the results obtained from only a few dogs. Bile salts will, however, cause cellular damage and edema when introduced into tissues foreign to these salts As a rule, as Rich and Duff pointed out, the irritating effect of bile injected subcutaneously does not produce the hemorrhage so characteristic of acute fulminating pancreatitis, but Dragstedt and his collaborators (1934) were quite convinced that the cytolytic and necrotizing properties of bile salts could account for any damage to the pancreas that followed the injection of bile into the pancreatic duct. They qualified that statement by suggesting that bile is probably more toxic in the presence of pancreatic enzymes, though they would not admit that the activation of trypsinogen by bile is the cause of the pancreatic damage. We are left with the impression that bile salts, despite their recognized cytolytic properties, require the help of pancreatic enzymes to wreak their full havoc on the pancreas.

Nonspecific Irritants Producing Pancreatitis It has been shown that a wide variety of irritating substances (acids, alkalis, oils, formaldehyde and others), when injected into the pancreatic duct, will also produce hemorrhagic pancreatitis, although not as uniformly and spectacularly as will bile. The manner in which they accomplish their mission also is not clear Usually the explanation points to their irritating effect on protoplasm and stops without revealing why the pancreas should react with such peculiar vehemence to their presence In addition to the irritating properties of these solutions, injection of them into the pancreatic duct by a syringe usually ruptures the duct system because of unphysiologic pressures. This rupture, according to Rich and Duff, is the vital point in their injurious effect, because it allows pancreatic enzymes to escape into the interstitial tissue and there become active and destructive On the other hand, mere rupture of the duct system by nonirritating solutions, such as saline or blood serum, will not result in pancreatitis

Ampullary Calculus We should briefly review the evidence supporting Opie's statement that an obstructing ampullary calculus initiates the reflux of bile. Opie in his enthusiasm cautioned the profession that a small gallstone might obstruct the papilla, initiate pancreatitis and then be passed into the duodenum before the surgeon or pathologist could find it. Even with this allowance, the clinical incidence of an impacted calculus in cases of acute pancreatitis is low, at the highest 10 per cent Schmieden and Sebening, reviewing 1,278 cases in Germany, reported an incidence of 4 4 per cent.

Spasm of the Sphincter of Oddi Confronted by the low incidence of ampullary calculus in acute pancreatitis, advocates of the biliary reflux theory turned in 1919 to Archibald's report that he could experimentally produce reflux of bile into the pancreas and acute pancreatitis as well, by causing spasm of the sphincter of Oddi. This was a new concept, in fact, the medical profession in general was not even aware that there was such a thing as the sphincter of Oddi, which comprises the muscle fibers encircling the duodenal tip of the common duct.

a large number of examinations have been catalogued and analyzed, but the knowledge already accumulated is most stimulating and promising. A recent report (1948) on the use of this procedure comes from France, where Mallet-Guy and others have analyzed their results in over 800 "radiomanometric" examinations of the biliary tree in an attempt to determine the frequency and causes of reflux into the duct of Wirsung during cholangiography. Because this technic represents the most logical and convincing method of investigating the possibility and significance of biliary reflux into the pancreatic duct, we shall discuss the results in some detail.

These investigators have analyzed 800 cholangiographic examinations (2,826 roentgenograms) performed by them until November 1947. About half of these examinations were done during operation and the rest postoperatively. Almost all were manometrically controlled. The operative cholangiographic examinations included only those in which the patient received no morphine preoperatively and in which the operative anesthesia was either local anesthesia of the abdominal wall or oxygen-ether inhalation They believed that operative cholangiograms are more valuable than postoperative studies, because they delineate the actual pathologic condition, unaltered by surgical treatment. Of the 800 examinations they reported 173 instances of reflux of lipiodol into the pancreatic duct, an incidence of 21 6 per cent. Scandinavian reports by Rudstrom (1944), Millbourn (1944), and Hjorth (1947), on large series of cholangiograms have revealed that reflux into the pancreatic duct occurred in 32 to 46 per cent of cases. They emphasized that from two to ten films may be necessary to demonstrate it radiologically.

Reflux, according to Mallet-Guy, is an abnormal condition, occurring only in the presence of disease either of the sphincter of Oddi or of the pancreas. Mirizzi, an Argentinian surgeon who has performed over 2,000 cholangiographic examinations, has agreed with this statement. The French authors believed that *no amount of pressure in a normal biliary tree with a normal pancreas could produce reflux of radiopaque solution into the duct of Wirsung.* In Table II are listed the causes of pancreatic reflux in Mallet-Guy's series of 173 cases. The low incidence of acute pancreatitis in reflux of radiopaque solution is significant, as is the number of cases without pancreatic disease, 96 in all according to operative findings. Of those 9 cases with an impacted ampullary calculus that showed radiologic reflux, in only 5 did the pancreas show evidence of inflammation at operation. In their experience the authors have never seen any direct ill effects consequent to reflux of radiopaque material Significantly, they regarded reflux as a symptom of malfunction In the 40 cases of chronic pancreatitis where the sphincter of Oddi functioned properly, the reflux into the pancreatic ducts was considered evidence of a "dystonia of the duct of Wirsung," which accompanied the chronic lesion. The authors advised sphincterotomy for hypertonic or spastic sphincter and unilateral splanchnicectomy for hypotonic sphincter (the sympathetic nervous system supposedly relaxes the sphincter of Oddi).

The Syndrome of Spasm of the Sphincter in Pancreatitis. In this country Doubilet, Colp, and various co-workers have been especially impressed with the importance of a spastic sphincter as a cause of recurrent pancreatitis. Acting on Archibald's original suggestion and proceeding on the assumption that reflux

apparatus which can produce any pressure desired by the addition of saline to the common duct (McGowan, Butsch, and Walters). Spastic sphincters may withstand very high pressures, up to 600 mm of solution (bile and saline) before suddenly relaxing, while hypotonic sphincters may prevent the perfusion pressure from rising above 10 to 20 mm. Characteristically, when the spastic sphincter relaxes, the biliary pressure falls sharply before it gradually builds up again. On the other hand, a fixed obstruction of the papilla, although rendering a high reading, will have no sharp breaking point, and, once that has been reached, the pressures remain at a plateau instead of falling sharply. These are some salient points which the manometric determination of biliary pressures can offer. Inasmuch as the whole concept of a spastic sphincter depends on the production of altered pressures within the common duct, that condition can be accurately diagnosed only by knowledge of those abnormal pressures, by such a means spasm of the sphincter of Oddi has been observed many times.

The Use of Cholangiography to Detect Sphincter Spasm. Knowledge of sphincteral function has fortunately been greatly expanded during the past 15 years by the increasing use of cholangiography, a series of roentgenograms or fluoroscopic examination of the bile ducts following injection of radiopaque liquid (most frequently lipiodol) directly into the extrahepatic biliary tree. This examination also can be performed only when this structure is exposed at operation or on patients who postoperatively carry catheters draining the common duct or gallbladder The procedure is extremely fruitful in revealing the causes and degree of common duct obstruction, especially those of a fixed nature. Tumors, stones, and strictures may be located and identified by their negative shadows. By its routine use postoperatively one can tell when bile is passing normally into the duodenum, the passage indicates in an exact manner when drainage of the common duct may be discontinued.

Aside from its great value in the diagnosis and treatment of lesions of the biliary tree, cholangiography has provided interesting information about sphincteral spasm On the basis of successive cholangiograms, one of which shows ampullary obstruction to the outflow of radiopaque material and the other of which does not, one can diagnose a possible functional spasm of the sphincter, but, in emphasis of what has already been stated, control of the pressure at which the radiopaque material is injected is necessary for accurate information about the functional status of the sphincter of Oddi.

Evidence of a Common Channel from Cholangiography. A second question which the manometrically controlled injection of lipiodol into the extrahepatic biliary tree can answer concerns the hitherto bitterly disputed point as to the possibility of biliary reflux into the pancreatic ducts of the living human. Archibald postulated that reflux of bile followed spasm of the sphincter, but he could not prove it. Cholangiography has shown that Archibald was correct. In the presence of a spastic sphincter, manometrically determined, lipiodol frequently flows into the pancreatic duct

The combined procedure of measuring intrabiliary pressure and at the same time of injecting radiopaque fluid has been used to some extent in this country, but much more frequently by foreign surgeons As yet, its application has been too short-lived to answer all the questions which potentially can be solved when

In regard to the efficacy of sphincterotomy in preventing reflux it should be noted that Mallet-Guy et al. (1948) found reflux into the duct of Wirsung in the presence of a hypotonia or abnormal relaxation of the sphincter. They explained this as a passive flow of medium, as in a "swamp," into the pancreatic duct unimpeded by the normal sphincter tonus. In fact, this happened in 6 of 14 cases who were examined by cholangiogram after sphincterotomy, according to the case reports of Doubilet and Mulholland (1948). Reflux thus may not always disappear after sphincterotomy.

In summary, spasm of the sphincter of Oddi can certainly occur. Probably it causes bile to flow into the pancreatic ducts. Possibly bile in this location causes pancreatitis. At present we can say little more.

Reflux of Pancreatic Juice into the Biliary Tree. As a corollary to the concept of reflux of bile into the pancreatic ducts, the reverse process, the reflux of pancreatic juice into the common duct and even into the gallbladder, has attracted increasing attention in recent years Wolfer among others in this country has stated that pancreatic juice forced into the gallbladder may cause cholecystitis. It is certain that in an appreciable number of patients, according to Popper (1933) 17 per cent, pancreatic ferments can be found in gallbladder bile either at operation or in bile that drains postoperatively. In a recent comprehensive review of this subject Hjorth (1948) believed that reflux of pancreatic juice was an important cause of cholecystitis and cholelithiasis In his own experiments he produced changes resembling cholecystitis in the gallbladders of 21 rabbits within five weeks to 13 months by injecting a small amount of active trypsin into the gallbladder This interesting possibility cannot be pursued further except to point out that the presence of pancreatic enzymes in biliary drainage is a valid proof of a common channel existing in those patients

Objections to Opie's Common Channel Theory The supremacy of Opie's common channel theory has not been uncontested throughout these years. In the main, the objections have fallen into three general groups: (1) those that doubt the frequent occurrence of reflux of bile into the duct of Wirsung on anatomic grounds, (2) those that do likewise for physiologic reasons; (3) those that believe that even if reflux of bile occurs, pancreatitis does not necessarily or even frequently ensue Although most of the work to be cited was done prior to the widespread use of cholangiography, the reader will see that this valuable tool has already given partial or complete answers to many of the questions raised

(1) Anatomic Evidence of a Common Channel from Postmortem Specimens A great many anatomic dissections of fresh and fixed specimens have been performed to clarify the exact relationship between the terminal ends of the common duct and main pancreatic ducts Because the mucous membranes of the ampulla of Vater are so delicate and pliable, the dissection is difficult to perform even after dyes have been injected into the pancreatic duct system, and this difficulty is reflected in the divergence of the reported anatomic findings. A survey of these reports, beginning with Schirmer's in 1893 and continuing to the present, reveals that three general anatomic relationships prevail, as indicated in Fig 4.

(A) The classically described ampulla of Vater receives the duct of Wirsung far enough up from the outlet into the duodenum that blockage of that

of bile into the pancreatic ducts causes pancreatitis, they have treated a number of such cases by section of the sphincter and have obtained encouraging results, although too brief a time has elapsed for final conclusions. They have shown by recording common duct pressures on a slowly revolving kymograph that hydrochloric acid placed in the duodenum by a tube will cause spasm of the sphincter of Oddi, which disappears after sphincterotomy. Morphine causes spasm of the

TABLE II

INCIDENCE OF THE PATHOLOGIC STATES ASSOCIATED WITH THE REFLUX OF RADIOPAQUE MATERIAL INTO THE DUCT OF WIRSUNG DURING CHOLANGIOGRAPHY.

(After Mallet-Guy et al, 1948)

Mechanical Obstacles		12
Cancer of ampulla of Vater	1	
Relative compression of the common duct by tumor of the pancreas	2	
Impacted calculus in ampulla of Vater	9	
Hypertonic Sphincter of Oddi		53
Without pancreatic lesions	40	
With chronic pancreatitis	13	
Hypotonic Sphincter of Oddi		36
Without pancreatic lesions	22	
With chronic pancreatitis	14	
Chronic Pancreatitis without Identification of Dystonic Sphincter		40
Without cholecystitis	23	
With cholecystitis	17	
Acute Pancreatitis		2
Nonobstructing Common Duct Syndromes		19
Common duct stone without obstruction	16	
Cholangitis with dilatation of main bile duct	2	
Unidentified	1	
Miscellaneous		11
Acute cholecystitis without dystonia of the sphincter	3	
Cholecystitis (no manometric control)	6	
Cholecystitis (no direct common duct manometric control)	2	
Total		173

duodenal wall, and therefore its effect in raising the pressure in the common duct does not disappear after sphincterotomy Cholangiograms on patients with pancreatitis have shown that reflux into the pancreatic duct often occurs during spasm of the sphincter Doubilet and Mulholland have believed that they prevent this reflux by sectioning the sphincter of Oddi Colp and Doubilet have even developed a special instrument for cutting the sphincter, which is designed to be passed down via the common duct and thus obviates opening the duodenum In contrast to Mallet-Guy, they apparently thought that reflux is a cause rather than a symptom or sign of pancreatitis

Perhaps in the next few years when the success of sphincterotomy in preventing recurrences of pancreatitis can be better evaluated, we shall be in a position to conclude from this clinical experiment whether spasm of the sphincter and reflux of bile into the duct of Wirsung are truly important in the etiology of pancreatitis.

duct a similarly high figure, 91 5 per cent, of common channels in the presence of an obstructed ampulla. These more recent cholangiographic findings have suggested that a common channel is possible in nine-tenths of the cases studied at necropsy, whereas anatomic studies usually indicated the possibility at between one-half to one-third or less.

(B) In this instance the pancreatic and common ducts enter the duodenum side by side at a common papilla, but do not form an ampulla of more than 2 mm. in length (no possibility of a common channel). Anatomic dissection studies have stated that this is common, from 12 to 45 per cent. According to postmortem cholangiography, it has been relatively rare, 4 to 6 per cent

(C) In this instance the main pancreatic and common ducts have separate openings into the duodenum (no possibility of a common channel). In dissected preparations this has been found in about 30 per cent. In postmortem cholangiograms it has occurred in 4 to 8 per cent.

It appears, then, that at postmortem examination, despite the low incidence of a possible common channel in dissected material, reflux of bile can progress into the pancreatic duct, and pancreatic juice can likewise flow into the biliary tree in a large proportion of cases, when the ampulla is obstructed mechanically. Before leaving this topic, we should point out that no one has yet reported a thorough investigation, either anatomic or cholangiographic, of the incidence of a common channel in cases of pancreatitis, either acute or chronic. A number of isolated cases of acute pancreatitis has been described in which the duct of Wirsung opened separately into the duodenum, thus ruling out the possibility of biliary reflux, but no indication of the frequency of separate openings in all cases of acute pancreatitis has been given.

(2) Physiologic Evidence of Biliary Reflux into the Pancreas: In connection with the second group of objections to the theory of bile as a cause of pancreatitis, there is considerable evidence to suggest that, even if anatomic relationships allow a common channel to form, physiologic mechanisms usually prevent a reflux Mann and Giordano (1923) stated that the maximum pressures within the common and pancreatic ducts are about equal. Since pancreatic secretion is especially active after meals, one would hardly expect a reflux of bile into the pancreatic ducts at that time, yet, attacks of pancreatitis frequently begin after a heavy meal

Harms (1927) in Germany after measuring simultaneous pressures in the pancreatic and biliary ducts stated that the pancreatic pressure was always higher than the biliary pressure in all phases of digestion. Dragstedt et al. (1934), however, re-emphasized that in ampullary obstruction the pressure in the pancreas may be lowered by a patent duct of Santorini, which then serves as an outlet for the whole biliary and pancreatic secretion and permits bile to flow through the pancreas. Hjorth noted a patent and communicating duct of Santorini in 29 per cent of 100 roentgenologic visualizations of the pancreatic duct system in cadavers.

(3) Effects of Sterile Bile in the Pancreatic Duct: A third group of observations indicates that even if bile does enter the pancreatic ducts at pressures

will allow a common channel to form Opie believed that this was possible in 77 per cent of 100 normal dissected specimens Cameron and Noble (1924), after artificially impacting a calculus in the ampulla and injecting the common duct with molten Wood's metal, believed that a common channel was possible in 66 per cent of 100 specimens. Howard and Jones (1947) by a similar technic, using dye instead of Wood's metal, put the

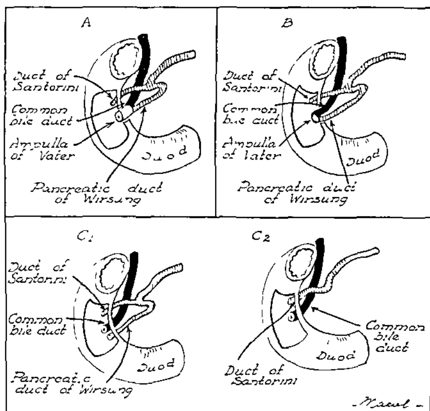


FIG 4 —Possible anatomic variations of the common bile duct and duct of Wirsung in relationship to the ampulla o[illegible] mon channel at ampulla o[illegible] into duodenum (C_2) Al[illegible] id

figure at 54 per cent Other dissectors have claimed this relationship to be probable in only 4 per cent (Mann and Giordano, 1923) or 30 to 40 per cent (Reinhoff and Pickerell, 1945). Hjorth (1947), believing that anatomic dissection is inaccurate and that the best proof of a possible common channel is to observe what happens when a test fluid is injected into the duct in the presence of ampullary obstruction, has performed postmortem cholangiography on 100 cases, in which the ampullary region appeared normal. By opening the duodenum and clamping the papilla so that the terminal 3 mm of the ampulla was obstructed, he injected radiopaque liquid into the pancreatic duct near the tail of the gland at low pressures (140 to 360 mm water) In 86 per cent of 100 cases he observed a common channel Millbourn (1944), also using cholangiography on 100 postmortem cases, found by injecting the common

OBSTRUCTION OF PANCREATIC DUCTS, AUTODIGESTION OF PANCREAS

The concept that an obstruction to the outflow of pancreatic juice causes damage to the pancreas springs from the same ancestral stock as does its cousin, the theory of biliary reflux. In both instances, the clinical observation in the 1890's that cholelithiasis is common in acute pancreatitis had given impetus to the formulation of these theories. As a matter of fact, continental writers originally explained this observation on the basis that a gallstone in the lower common duct might obstruct the terminal outlet of the duct of Wirsung, thereby blocking secretion and initiating pancreatic damage.

Opie's Belief in Obstruction of the Pancreatic Ducts as a Cause of Pancreatitis. In 1900 Opie reported that after ligating the pancreatic ducts of cats he found fat necroses in and about the pancreas, and if he gave the cats pilocarpine to stimulate secretion during and after the operation, the fat necroses became more widespread. Despite these positive results he was honestly disturbed that mere ligation of the pancreatic duct gave no hemorrhagic necrosis but only fat necrosis in the parenchyma. While bearing in mind this objection to his own work, he nevertheless proceeded along the same lines for lack of better evidence, and only four months before the appearance of his report enunciating the common channel and biliary reflux theory (1901), Opie published an extensive clinical analysis on "The relation of cholelithiasis to disease of the pancreas and to fat necrosis," in which he collected from the literature 31 cases showing acute pancreatitis and gallstones and added a postmortem case of his own, a patient who had died with acute hemorrhagic pancreatic necrosis and had had a stone in the terminal common duct Opie explained the disease by saying, "one may fairly assume that the primary cause of the lesions in and about the pancreas was an interference with the outflow of pancreatic secretion."

Why then did he suddenly change his mind three months later and abandon an opinion built on four or more years of clinical and experimental work? Although he did not publicly explain the reason for his shift in beliefs, it would seem logical that he changed because experimentally he was able to produce acute hemorrhagic necrosis by injecting bile into the pancreas, whereas he could not do so if he merely obstructed the outflow of pancreatic juice. Being a keen and honest observer, he was willing to alter his ideas in the face of new facts instead of hiding them from view with theoretical camouflage. If one reads his book carefully (1910), written when the reflux of bile was considered the world over as the most significant cause of pancreatitis, one finds that even then Opie did not give up entirely his earlier conclusions. We have discussed Opie's views and reactions in some detail because we believe that they may serve to emphasize the vital necessity of an open mind for anyone interested in the etiology of pancreatitis

Obstruction of the Pancreatic Ducts and Activation of Trypsin in Acute Pancreatitis Following the birth and rapid growth of the bile reflux theory, the concept of pancreatic duct obstruction as a cause of pancreatitis became overshadowed and hidden, especially because it did not particularly appeal to clinicians In 1936 it returned to prominence as the result of a thoughtful investigation by Rich and Duff on the problem of acute pancreatitis. Impressed by certain objections to the theory of biliary reflux, they endeavored to find a

consistent with those occurring in the body, no particular damage to the pancreas follows. Nordmann (1913) ligated the papilla of Vater on its duodenal side in cats, thus creating a common channel. Although he observed jaundice, he found no pancreatitis unless he infected the bile by adding various bacteria. Mann and Giordano (1923) performed the same experiment in goats and likewise did not obtain pancreatitis. Furthermore, they injected sterile bile into the pancreatic ducts of dogs at a measured pressure and never produced pancreatitis at any pressure less than 800 mm. of water, well above the pressure that can occur in the common duct Wangensteen et al. (1931), after creating a common channel in cats by Nordmann's method, did not observe pancreatic damage unless they stimulated the gallbladder by injecting air into it or by feeding the cat a fatty meal Under these circumstances they observed changes in the pancreas, including acute pancreatitis, in over half of their cats.

Incidence of Cholelithiasis in Acute Pancreatitis. What has been stated above constitutes only a small amount of the experimental efforts with regard to the theory of biliary reflux, but probably in the last analysis most clinicians believe that bile somehow plays an important part in the pathogenesis of acute pancreatitis. This impression no doubt arises from the impressive frequency with which acute pancreatitis is accompanied by disease of the gallbladder (including cholelithiasis) The continental writers before the turn of the century (Korte, Oser, Lanceraux) were aware of this connection, and Opie based the mechanism of his common channel theory on the assumption of a coexisting biliary tract lithiasis. Practically all authors since then have stressed the high incidence of gallbladder disease in pancreatitis Clinical reports have stated that this varies from 40 to 70 per cent (Paxton and Payne, 1948, 41 per cent, Morton, 1945, 62 per cent, Schmieden and Sebening, 1927, 69 8 per cent) The most complete postmortem survey on this subject comes from the University of Minnesota, where Molander and Bell (1946) reviewed 41,333 necropsies and found 158 cases of acute pancreatitis One-third of the male cases and two-thirds of the female cases carried gallstones as well, which is six times the incidence of cholelithiasis in the general population. Although acute pancreatitis is commonly accompanied by extrahepatic biliary tract disease, the reverse is not necessarily true, according to Wiener and Tennant (1938), who in a series of 4,000 necropsies found 343 cases of extrahepatic biliary tract disease, among which acute pancreatitis was no more common than in the entire series of 4,000 autopsies.

Cases of Pancreatitis without Biliary Tract Disease These figures leave us with from one-third to one-half of the cases of acute pancreatitis that give no evidence of coexisting biliary tract disease, as even the most ardent advocates of the common channel theory admit, although at the same time they dismiss these cases from serious consideration In this connection, Comfort and co-workers have repeatedly emphasized a group of patients with recurrent pancreatitis in which no biliary tract disease can be found In an effort to account for this discrepancy other theories and evidence have been advanced which offer valuable information about the disease, yet each in turn leaves unheeded or poorly answered a sizable group of questions that remains to puzzle the critical mind. We shall briefly note these theories and their deficiencies, inasmuch as the whole answer may be derived from a variety of sources.

(1948) after much experimental work over a period of years have concluded that pancreatic edema can be produced fairly consistently by ligating the pancreatic ducts and administering a dose of secretin, but they have never been able to cause pancreatic necrosis by this means. In order to change pancreatic edema induced by duct ligation into necrosis, they had to superimpose temporary occlusion of the main pancreatic artery upon obstruction of the pancreatic duct. From these findings they assumed that a relatively benign transient edema of the pancreas may be transformed by temporary local ischemia into hemorrhagic pancreatic necrosis.

A recent paper (1948) by Lium and Maddock categorically stated in its conclusion, "acute pancreatitis is the result of ductal obstruction in an actively secreting pancreas" These writers' conclusions were based on experiments almost identical with those performed by Opie in 1900, described above. Like Opie, they ligated the pancreatic ducts of cats and found in the pancreas fat necrosis and some mild cellular infiltrate, which was intensified by administering pilocarpine or secretin. Also like Opie, they found no hemorrhage nor gangrene, but instead of facing this potent objection, they explained it by saying that the cat's pancreas is different from the human gland and proceeded to their unqualified conclusion.

A more impressive indication of the importance of pancreatic duct obstruction is based on the behavior of the serum amylase after ligation of the pancreatic duct. Even though ligation of the ducts does not cause hemorrhagic pancreatitis, numerous investigators have found that the serum amylase mounts rapidly after this procedure, remains elevated for several weeks, and then falls (Goldstein et al., 1946). If mecholyl and secretin are given after ligation to stimulate pancreatic secretion, the abnormal rise in serum amylase is quite remarkable (Popper et al., 1943) Although an abnormally high serum amylase does not necessarily signify acute pancreatitis, it does indicate pancreatic dysfunction. What relation this dysfunction in acute pancreatic obstruction bears to acute pancreatitis is not well understood

Objections to Pancreatic Duct Obstruction as a Cause of Acute Pancreatitis. A variety of clinical experiences causes hesitation in accepting the notion that mere obstruction of the flow of pancreatic juice will cause acute pancreatitis. So far as gross obstruction of the duct is concerned, acute pancreatitis is rare in carcinoma of the head of the pancreas, even though the ducts be widely dilated A case of acute hemorrhagic pancreatitis occurring in the presence of an ampullary carcinoma which caused obstruction of the pancreatic ducts has been reported by Puestow et al. (1946) Following surgical procedures on the pancreas, where the head of the gland has been resected and the ducts ligated, acute pancreatitis is rare. Brunschwig and Whipple have independently made a point of this fact in urging that the ducts can be ligated without danger of acute pancreatitis supervening. In confirmation of experimental observation of the rise in serum amylase after obstruction of the pancreatic ducts, Naffziger and McCorkle (1943) likewise found a rise in serum amylase after partial resection of the head of the pancreas for carcinoma, neither of their 2 cases, however, developed acute hemorrhagic pancreatitis As for microscopic obstruction of pancreatic secretion, the clinician has no way of knowing when metaplasia of

common denominator in acute pancreatitis in postmortem examinations. They discovered a "specific vascular lesion," a necrosis of the walls of the small blood vessels, which they attributed to the action of trypsin. To check that assumption they were able to produce the same vascular lesion with hemorrhage by injecting trypsin subcutaneously in dogs They next established that the injection of any solution into the pancreatic duct ruptures the duct system with great ease and allows the injected material to escape into the interstitial tissue. They believed that pancreatic juice, rich in trypsin, as after a meal, might be forced into the interstitial tissue of the gland if there were obstruction to the outflow of the juice Once outside of the duct system, trypsin can become activated by tissue juices and thereafter can initiate the specific vascular lesion, which causes the hemorrhage characteristic of the disease. They believed that in their postmortem examination of cases with acute pancreatitis obstruction of the pancreatic duct system was frequent (in 23 of 24 cases). Such obstruction may result from gross blockage of the duct of Wirsung by ampullary stone, pancreatic calculus, tumor, or scarring, but most frequently is produced by microscopic lesions, metaplasia of the epithelium in the small ducts The epithelium becomes so exuberant that it clogs the lumen and traps secretion. These microscopic changes may cause the obstruction that forces trypsin into the parenchyma and sets off the train of events leading to acute pancreatitis.

The Role of Trypsin in Pancreatitis The role of trypsin, as emphasized by Rich and Duff, is not a new concept. Ever since Langerhans in 1891 demonstrated that pancreatic lipase caused the lesions of fat necrosis, others have postulated, following Klebs' suggestion in 1870, that trypsin was responsible for the unusual necrosis to which the pancreas is alone susceptible The concept of autodigestion gained strength from the discovery of enterokinase by Shepovalnikov, for then it was supposed that duodenal contents regurgitating up the duct of Wirsung could activate trypsin within the gland and cause autodigestion. Although experiments simulating this situation were not uniformly successful in producing acute pancreatitis (Williams and Busch, 1907), the idea that the intraglandular activation of trypsin is responsible for the acute lesion has great appeal. The supposition that bile, or bacteria, or trauma, or tissue juices can activate trypsin, allows this idea to fit into any of the current theories on etiology. Dragstedt (1934) went to considerable pains to argue that active trypsin plays no role in the pathogenesis of pancreatitis, but his evidence was suggestive rather than conclusive. Other arguments against the importance of active trypsin showed that if it was injected into the pancreatic ducts in small amounts without rupturing the ducts no damage followed, and that if active pancreatic juice escaped into the peritoneal cavity (Senn, Dragstedt), no lesions were produced While these conflicting experiments give rise to confusion, they do not exclude the fact that trypsin under certain circumstances and in certain localities may be injurious. The work of Rich and Duff represented the first well controlled effort to demonstrate the destructive effect of active trypsin on the pancreas as well as on other tissues. Unfortunately, their explanation of how trypsin becomes activated within the pancreas is not as convincing as their proof of its damaging qualities.

Recent Observations on Pancreatic Duct Obstruction. Popper and co-workers

or, as occasionally reported, pancreatitis following debilitating diseases such as typhoid fever, it is quite obvious that the inflammation is started by a blood-borne agent, but in this discussion we are concerned with the majority of cases, in which the etiology is not so clear.

Even before the importance of cholelithiasis in pancreatitis had been clinically established, Fitz in his original monograph on pancreatitis noted that many of his patients suffered from "gastroduodenitis" and suggested that perhaps bacteria from the inflamed duodenum made their way into the pancreas and caused the inflammation. During the 1890's, European investigators (viz., Hlava, 1895) noted that if the injection of injurious substances into the pancreatic duct was contaminated with pathogenic bacteria, the pancreas more frequently succumbed to acute pancreatitis, but organisms from clinical cases could not be obtained with reasonable frequency and specificity. This objection remains today as the chief obstacle confronting a bacterial theory of the causation of pancreatitis. Another objection stems from the fact that the pathologic picture of the typical disease shows a predominance of parenchymal necrosis rather than the cellular infiltration characteristic of bacterial inflammation. When suppurative pancreatitis supervenes, no one questions the importance of infection in the process, although many would claim that suppuration secondarily follows an originally sterile necrosis.

Experimental Evidence of Bacteria in Acute Pancreatitis. The advent of the notion that chemical agents such as bile or pancreatic ferments were responsible for the peculiar pancreatic lesions tended to lessen the importance of the bacterial theory, but it has gained impetus from various clinical and experimental findings. Both Nordmann (1913) and Archibald (1919) were unable to produce acute pancreatitis in cats unless they used infected bile. Dragstedt et al. (1934), who considered bile the most important factor in the origin of acute pancreatic necrosis, were nevertheless impressed with the importance of bacteria in causing the toxic manifestations of the disease. Their findings indicated that anaerobic, gram-positive organisms, similar to *Cl. welchii*, normally exist in the rabbit's and dog's pancreas The toxins elaborated by these organisms, which grow rapidly once bile has initiated necrosis, are responsible for the lethal aspects of pancreatitis Dragstedt believed that sterile products of pancreatic necrosis were harmless to the body if placed intraperitoneally

Experimental Cholecystitis Does Not Cause Acute Pancreatic Necrosis. In general, however, experimental workers either dismiss the bacterial theory lightly or give evidence of its slight importance Wangensteen et al. (1931) established acute infections in the gallbladders of cats by a variety of means, and although they sometimes observed "a loss of definite contour of the pancreatic acini with an edema or swelling of the interstitium," they never found hemorrhage, pancreatic necrosis, or fat necrosis. When they injected bacteria into the pancreatic substance, they likewise failed to produce necrosis Bacteria placed in the pancreatic duct do not cause pancreatitis.

Clinical Evidence of Infection in Acute Pancreatitis. From a clinical standpoint it is interesting that while pancreatic necrosis is frequently accompanied by chronic gallbladder disease it rarely is seen with acute cholecystitis, in which instance the regional lymphatics should be most inflamed. Furthermore, contro-

the duct epithelium is present, but the surgeon and pathologist frequently observe in the pancreas focal scarring which must be as effective as metaplasia in causing obstruction in the small ducts, yet this focal fibrosis does not seem to be particularly associated with acute pancreatic necrosis.

Experimental Objections to Pancreatic Duct Obstruction as a Cause of Acute Pancreatitis Tying off the pancreatic duct is a commonplace laboratory procedure, and no one has observed pancreatic necrosis or hemorrhage as a significant complication of that procedure, except to note the presence of one or two small fat necroses about the ligature Senn of Chicago in 1886 performed extensive experiments on dogs to show that the pancreas can be subjected to a variety of traumatic procedures without endangering the life of the animal. After ligating a portion of the gland he observed atrophy and fibrosis wherever function had been impaired by the obstruction Numerous observers have repeatedly stressed the changes that follow ligation of the pancreatic ducts In brief, the secretory cells gradually disappear over a period of six to eight weeks and are replaced by a low grade inflammatory response, consisting of fibrous tissue and a few round cells This picture is entirely different from that of acute pancreatic necrosis. Banting, taking advantage of the long-established observation that following ligation of the duct acinar cells are replaced by scar tissue while the islands of Langerhans remain practically intact, was able to prepare his first extract of insulin from a pancreas treated in such a manner, and the development of acute pancreatitis in those glands did not thwart his brilliant experiment. The changes reported by Opie, Lium and Maddock, and others were observed in animals within a day or two following ligation, and they represent, no doubt, the early stages of the lesion which at a later date becomes extensive atrophy and fibrosis of the secretory parenchyma. De Takats (1929) has given a complete and careful histologic picture of the process following ligation of a portion of the tail of the pancreas drawn from observations taken from two days to a year postoperatively

Duodenal Diverticulum as a Cause of Pancreatic Duct Obstruction. Rarely, *a duodenal diverticulum involving the papilla of Vater may be associated with* pancreatitis, acute or chronic, and its presence, although usually harmless, should warn the clinician of the possibility of pancreatitis Ogilvie (1941) saw 3 cases of acute pancreatic necrosis associated with duodenal diverticulum and believed that obstruction of the pancreatic ducts was responsible for the acute disease.

In brief, although obstruction of the pancreatic ducts may play an etiologic part in some cases of acute pancreatitis, it is not, as understood today, a minor factor in and of itself. To be effective it requires the help of some other predisposing cause Active trypsin is probably implicated in some manner in the onset of acute pancreatic necrosis

Bacterial Infection

The connection between disease of the pancreas and biliary tract inflammation can be explained on still another basis, namely, the invasion of the gland by pathogenic bacteria via lymphatics or blood stream from a neighboring focus. In instances of metastatic abscess in the pancreas, pancreatitis following mumps,

contemporaries he believed that a rupture of the pancreatic arteries had resulted from a vascular lesion, most probably arteriosclerotic and perhaps syphilitic. Later experience has shown that neither syphilis nor, in all probability, arteriosclerosis, are significant entities in acute pancreatitis.

A great deal of work by various European investigators before 1900 attempted to show that thrombosis or embolism in the pancreatic vessels might induce acute pancreatitis. Smyth (1940) has reviewed these experiments. Hemorrhagic lesions were produced either by injecting substances such as wax, lycopodium, or oil into the pancreatic vessels so as to produce embolism, or by causing mass ischemia of a portion of the gland by excluding all blood supply. Because of the rich blood supply of the organ mere ligation of an artery will not induce pancreatic necrosis, whereas ligation plus injection of an embolic substance frequently does. The use of mass ligatures to cut off all blood supply to a portion of the gland is also an effective means of causing hemorrhagic necrosis in the infarcted area. Since 1930 certain continental authors have stressed that nervous reflexes, acting on the pancreatic vessels, may produce changes that lead to vasoconstriction and pancreatic necrosis, and lately Popper et al. (1948) have stated that local vasoconstriction in the presence of pancreatic edema probably gives the combination of factors that initiate hemorrhagic necrosis.

Despite suggestive material, the study of the disease in humans has failed to produce a significant etiologic factor that might be responsible for vascular changes unless one accepts the "trypsin" lesion described by Rich and Duff. Smyth, in an attempt to put the vascular theory on a sounder clinical basis, reviewed 40 necropsy cases with a particular search for vascular lesions. In only 11 of 40 cases could he find small changes in arteries and veins, corresponding to the "specific vascular lesion" of Rich and Duff, which he considered to be a result of the pancreatitis or concomitant with it but of no etiologic significance. After his study he was forced to say: ". . . any conclusions regarding the genesis of pancreatic necrosis based on a study of autopsy material must at best be speculative, for one is dealing with end stages. Evidence of responsible factors may well have been destroyed early in the course of the disease, without leaving a trace" By injecting emboli of metallic mercury into a pancreatic artery Smyth succeeded experimentally in creating infarcted foci of hemorrhagic necrosis but no fatal disease and no spreading lesions. The stage of secretory activity after stimulation with mecholyl and physostigmine had no effect on the degree of damage Recently more clinical attention has been paid to vascular factors. Johnson and Davis (1945) in an analysis of 22 cases believed that in 4 instances vascular occlusion associated with hypertension precipitated attacks of acute pancreatitis When "abdominal angina" occurred in hypertensive, arteriosclerotic individuals, they suspected acute pancreatitis. Paxton and Payne (1947) noted hypertension in 19 5 per cent of their 307 cases and pointed out that since the average age of their patients fell in the fifth decade, arteriosclerosis was not prominently associated with the hypertension.

More experimental work is needed to elucidate what mechanism, if any, can produce a vascular lesion and whether a vascular lesion, once present, can in turn be the causative factor in pancreatic necrosis.

versy exists as to whether lymphatic flow can occur from the gallbladder to the pancreas. Kaufmann (1927) doubted that it could. Deaver (1921), one of the most ardent clinical champions of the infectious origin of pancreatitis, made a great point of the enlarged, inflamed lymph nodes which he found neighboring on the acutely diseased pancreas, but others have stated that these inflamed nodes are secondary rather than primary to the pancreatitis. Recently a provocative report by Koller from Sweden (1947) discussed 2 fatal cases of acute, edematous, nonpurulent, interstitial pancreatitis caused by eating food poisoned with hemolytic streptococci. Necropsy in both cases showed numerous gram-positive cocci in short chains in the pancreas. The author pleaded for more accurate bacteriologic studies in cases of acute pancreatitis

Such bacteriologic studies as have been made in large series of clinical cases do not indicate a marked importance of bacteria except in obvious instances Schmieden and Sebening (1928), in reviewing the records of 1,278 cases of pancreatitis, noted that among 187 cases cultured the peritoneal exudate was sterile in 84 instances, staphylococci and streptococci predominated in the infected cases. Among 94 cases the bile was sterile in 40, and in the remainder *B coli* was most commonly cultured. Other less extensive surveys have revealed various cases of acute pancreatitis yielding positive cultures from the pancreas, peritoneal fluid, or bile The role of inflammation is especially apparent when purulent pancreatitis accompanies suppurative lesions of the liver or biliary tract, but this type of pancreatic inflammation differs from the classical type, which shows necrosis and hemorrhage According to the literature since Fitz first observed the phenomenon, the mortality in purulent pancreatitis is notably less than in the more usual form of the disease.

It is probable that the edematous pancreatitis noted by Wangensteen in dogs with cholecystitis, the swollen head of the pancreas often observed clinically during operations for inflammation of the biliary tree and the cases of edematous pancreatitis with hemolytic streptococci reported by Koller represent true bacterial infection of the gland The pathologic picture in these cases appears to differ from that of necrosis and hemorrhage which characterize the typical clinical picture of acute pancreatitis According to Elman, who used the serum amylase test and clinical findings as diagnostic criteria, edematous pancreatitis, a relatively mild and self-limiting lesion, is by far the most frequent condition responsible for attacks of acute pancreatitis. Since this lesion rarely calls for operation or necropsy, we have no way as yet of estimating the frequency with which bacteria may be involved in this change Until more definite bacteriologic evidence is forthcoming, the bacterial theory remains only an interesting possibility among the causes of pancreatitis

VASCULAR FACTORS

One of the first pancreatic lesions to impress the authors of the nineteenth century was massive and sudden hemorrhage into the pancreas, "pancreatic apoplexy," a state analogous in their minds to cerebral hemorrhage. Fitz (1889) carefully distinguished between this condition and hemorrhagic necrosis of the gland, because he believed their etiology to be different. In common with his

blood amylase levels in 2 patients after resection of a carcinoma in the head of the pancreas. One patient developed a postoperative pancreatic fistula, but neither showed clinical signs of pancreatitis. As in the case of accidental trauma, surgical injury to the pancreas rarely causes clinical pancreatitis but may *frequently elevate the serum amylase.*

MISCELLANEOUS ETIOLOGIC FACTORS

Reflux of duodenal contents into the pancreatic ducts has often been stated to be a possible cause of pancreatitis, though without strong proof. The injection of duodenal contents into the pancreatic ducts has been shown to induce acute pancreatitis, but Williams and Busch (1907) objected to this evidence on the grounds that the duct system was ruptured. They were *unable to produce* acute pancreatitis with regularity by injecting small amounts of sterile enterokinase, and thus the fact that duodenal juice, forced into the pancreatic duct by duodenal peristalsis would activate the intraglandular trypsin and cause pancreatitis was rendered unlikely What, then, about passage of infected duodenal contents into the pancreatic ducts? *We have seen that instillations of bacteria* into the pancreatic duct will not induce serious consequences. Furthermore, it seems unlikely that duodenal contents can be forced into the pancreatic ducts. Archibald (1919), even with pressures of 1000 mm. of water, was unable to drive fluid from the duodenum into the pancreatic ducts.

Opie, however, used this mechanism to explain instances where acute pancreatitis had been localized about the duct of Santorini, the outlet of which has no sphincter. Occasionally a report of acute pancreatitis following obstruction of the lower duodenum is found, but such cases constitute no more than suggestions that duodenal reflux into the pancreatic ducts may have occurred. This mechanism, however, may exist more frequently than supposed Walters and Marshall have reported 4 patients who after swallowing methylene blue *discharged some of the dye in bile draining from their* common ducts after cholecystectomy. In all 4 patients the sphincter of Oddi had been widely dilated by stones, and pancreatic juice was found in the biliary drainage of 2 of the patients. Since the ferments might have come via the duodenum, we cannot assume that duodenal contents also flowed into the pancreatic ducts, but certainly the possibility existed. None of these *patients had pancreatitis.* Another rare entity has proved that duodenal contents can make their way into the pancreatic duct. *Schmieden and Sebening* have collected 50 cases, in which an Ascaris worm had invaded the duct of Wirsung and caused acute pancreatic necrosis

The history of an alcoholic spree or chronic *alcoholism* has preceded attacks of acute pancreatitis in enough instances to attract the attention of medical authorities No one has shown how alcohol provokes the pathologic changes, but it has been postulated that the beverage stimulates greater secretory activity of the gland in a manner similar to a large meal. A recent clinical survey of 307 cases of acute pancreatitis by Paxton and Payne (1948) revealed alcoholism in 18 per cent. Occasionally patients believed to be in an alcoholic stupor are in reality in shock from acute pancreatic *necrosis.* Weiner and Tennant (1938) were impressed by the high incidence of alcoholism (about 33 per cent of cases)

TRAUMA

Mechanical injury to the pancreas, either accidental or surgical, can be followed by acute pancreatitis, but in any group of cases a history of preceding trauma is unusual—less than 1 per cent in Paxton and Payne's series. During the recent war an occasional instance of pancreatic necrosis or cyst was reported as a complication of penetrating wounds of the epigastrium; and even nonpenetrating trauma to the upper abdomen may induce pancreatic damage. Shallow and Wagner (1947) have described the case of a boy who, after sustaining a blow in the epigastrium from the handle bars of a bicycle, developed clinical signs of acute pancreatitis and an elevated serum amylase, which became most marked nine days after the accident. Naffziger and McCorkle have pointed out that an elevated blood amylase frequently follows injury to the pancreas. They reported abnormal elevations in each of 7 cases of traumatic injury to the pancreas, 5 of which resulted from nonpenetrating blows to the upper abdomen. The maximum amylase values, varying from 241 to 2,117 Somogyi units, did not necessarily parallel the degree of injury. None of these cases actually developed acute pancreatic necrosis, although at operation 2 showed small fat necroses about the pancreatic wound, and it is safe to say that without the use of a serum amylase test these patients would not have been considered as suffering from acute pancreatitis. If we diagnose acute pancreatitis only on clinical grounds, it is probably uncommon after pancreatic trauma, but, if we use an elevated serum amylase as our diagnostic criterion, undoubtedly acute pancreatitis is much more frequent after injury than formerly thought.

Senn demonstrated to his own satisfaction that the dog's pancreas could endure crushing, tearing, ligation, partial excision, and a wide variety of surgical injuries without serious consequence to the animal except for eventual fibrosis of the traumatized gland. At the same time he was aware that the mere escape of pancreatic secretion as a result of trauma or even after opening the duct of Wirsung into the peritoneal cavity caused no digestion of the involved tissues. Many investigators have since confirmed these results (Flexner, 1900, Wagensteen, 1931). Small specks of fat necrosis frequently arise near the site of trauma but only rarely a true hemorrhagic necrosis supervenes.

Despite the relative immunity of the pancreas to experimental trauma, surgeons have been embarrassed by the onset of acute pancreatitis following operative procedures in the region of the pancreas frequently enough to make them chary of traumatizing the gland any more than is strictly necessary. Schmieden and Sebening in their extensive review listed 145 instances of pancreatic disease (necrosis, abscess, fistula) that followed operation: after gastric surgery, 91 cases, after biliary surgery, 38 cases, after splenectomy, 7 cases, after biopsy of pancreas, 4 cases. These authors were somewhat pessimistic about the further progress of pancreatic surgery, especially with regard to resection of tumors, because of the danger of postoperative pancreatic necrosis. Since 1936, when Whipple described a method for resecting carcinoma of the head of the pancreas, it has been shown that this complication is not to be feared, and surgeons today do not hesitate to approach the pancreas for valid reasons. Lewison (1940) mentioned a case of acute pancreatitis following resection of an ampullary tumor. Naffziger and McCorkle (1943) reported elevated

The affected portion of the pancreas is pale, swollen, and firm, being distended with interstitial fluid. The parenchyma is intact throughout with no soft or cystic areas. The color shows that the blood supply is still intact, although potentially endangered if the hard swelling continues. If the vessels are markedly congested, the swollen gland may be flaming red, but this does not mean hemorrhage. A cut section through the swollen portion reveals no pus. This gross picture of early inflammation is similar to that in almost any part of the body. Microscopically, it likewise is not unusual. Edema is evident in the interlobular connective tissue and perhaps among the acini. A few or many white cells, either polymorphonuclear or round cells, float in the fluid, and, when dense, they may lie between the acini themselves without seeming to damage the parenchyma Bacteria are not present by staining technic. The parenchymal cells appears normal. The neighboring lymph nodes may or may not be swollen and injected.

How the pancreas becomes edematous is not known. Many agents when introduced into the gland may cause this appearance: bacteria, trauma, chemical irritants, and bile. No specific etiologic factors of clinical note distinguish this type, except that pancreatitis following mumps probably takes this form.

Once established, what course does the edematous inflammation follow? It usually subsides within a week to ten days, according to Elman. This resolution occurs spontaneously and leaves little or no fibrosis, depending upon the severity of the edema. In a small number of cases for some unknown reason the edema gives way to hemorrhage, necrosis, or suppuration instead of disappearing. One cannot predict when this unfortunate sequence will occur, although presumably the chances are greater with severe edema. Once these changes have appeared, a permanent damage to the parenchyma usually follows, and the anatomic injury is greater Fat necroses may or may not accompany edematous pancreatitis Their presence tends to indicate a greater severity of the disease, but they may be absent in marked edema and obvious in the milder form.

Edematous pancreatitis is considered a relatively benign and transient lesion. Histologically that view is understandable, because no irreversible changes occur. The process frequently is found incidentally during laparotomy, especially for cholecystitis, and surgeons have long been aware that it tends to disappear spontaneously, leaving no trace at later operation or necropsy.

Prior to the widespread use of the serum amylase test, when edematous pancreatitis could be diagnosed only by the surgeons and pathologist, it was recognized only in its more severe grade, and although clinicians realized that it carried a lower mortality than other forms of the disease, it was still considered a serious affliction Schmieden and Sebening noted that 45 per cent of 1,278 cases of acute pancreatitis showed edema, with or without fat necrosis Those without fat necrosis, one-fifth of the group, carried a 24 per cent mortality, while of those with fat necrosis 60 per cent died. McWhorter's series, reported in 1932, yielded a slightly lower but still formidable mortality of 25 per cent in the edematous form. Zoepffel (1922), who first called attention to the clinical importance of this lesion, considered it to be the forerunner of the later more dramatic changes which had attracted the attention of Fitz, Opie, and others However, since our diagnostic power has been broadened by the

in a series of necropsies on patients with acute pancreatitis, and Clark (1942) has described the postmortem pancreatic lesions in 36 known alcoholics. He found pancreatic lesions in 18 per cent of 150 consecutive necropsies on alcoholics. These observations indicate that in some unknown manner alcoholism sets a favorable stage for acute pancreatitis

Whenever mystery shrouds the etiology of a particular disease, an *allergic* explanation is usually offered sooner or later, acute pancreatitis is no exception. Its catastrophic onset lends itself to the interpretation that it is a local anaphylactic reaction in the pancreas with exudation of serum and blood. Theoretically this occurs when the pancreas has been sensitized by biliary tract disease, trauma, alcohol, obesity, arteriosclerosis, and gastroduodenitis. Brodie and Ficarra (1944) have reported a case which suggests that acute pancreatitis may have followed the injection of sodium morrhuate for the treatment of varicose veins. There is little to support this anaphylactic concept.

After traveling a tortuous and frequently misleading path through a host of ideas and facts in search of a complete etiologic concept, we find that we still have no conclusive answer to the question Table I illustrates the various hypotheses which have been advocated. It has been revealed that blind adherence to a single theory will not solve the problem, but willingness to combine any of the known facts with fresh data will probably lead closer to the ultimate understanding of the etiology of pancreatitis.

PATHOLOGY OF PANCREATITIS

Our knowledge of the pathologic changes in acute pancreatitis is not complete. We are well aware of the end stages, but as yet pathologic studies have not allowed us to understand the very first changes in pancreatitis, and until we do so, our treatment must remain for the most part on empirical grounds. Unfortunately, as Smyth has emphasized, material based on postmortem studies has hidden this valuable information about the early changes under the devastation of necrosis, hemorrhage, and pus, and for the present only the description of what has been seen at operations and postmortem examinations is available.

For descriptive purposes, five grossly different pictures are seen in acute pancreatitis, although they rarely exist singly in pure form. Their anatomic differences do not imply different pathogenetic backgrounds, and just how much they can be considered part of a common process is hard to determine. Undoubtedly there is close relationship between some of the forms, but on the other hand there may be little between others

The common parenchymal lesions seen early in the clinical course of acute pancreatitis are. (1) edema, (2) hemorrhage, (3) necrosis, (4) suppuration, and (5) fat necrosis.

Edema

Edema is probably the most frequent phase of the disease. Areas of edema develop in any part or in all of the gland. The head is the most frequent site, but isolated spots in the tail, body, and uncinate process are not uncommon.

acute hemorrhagic pancreatitis found evidence of thrombosis in 26. The thrombosis involved veins more frequently than arteries, was both recent and organized, and was not always located near an area of necrosis. After careful studies Smyth concluded that there was no way of determining whether fresh thrombi had formed before or after necrosis Rich and Duff (1936) have described in great detail a vascular lesion of both arteries and veins that leads to rupture and hemorrhage but is not particularly associated with thrombosis. Microscopically it is distinguished by necrosis of the media of the vessel similar to that of renal arteriolar necrosis. They "were struck by the constant presence" of this lesion in their cases without giving actual figures. Subsequent studies have not completely confirmed their findings. Smyth noted the same lesion in only 11 of his 40 cases and considered it nonspecific. Clark (1942) examined the bodies of 36 alcoholics with pancreatic lesions and found interstitial hemorrhage in 16 organs. He stated that "necrosis of the vessel wall" usually accompanied this bleeding "Necrosis" is not further clarified by the author. Rogers (1944) has described 2 cases of acute pancreatic necrosis with vascular lesions similar to those described by Rich and Duff; but he considered them as evidence of primary disease of the blood vessels and connective tissue, comparable to that found in such poorly understood states as periarteritis nodosa.

Hemorrhagic lesions are serious manifestations. As one of the two anatomic signs of acute pancreatic necrosis, hemorrhage carries a high mortality—70 per cent according to Morton (1945). It denotes severe pancreatic damage In those cases surviving mild and moderate bleeding, the pancreas can apparently resorb the blood to a large extent Red cells which have accumulated in softened and cystic spots naturally cannot be so completely removed, and the dead material remains stained brownish-black and later grayish-yellow. Fitz noted that in persons who died shortly after the onset of acute pancreatitis the pancreas was bloody and red, while in those succumbing about ten days after the onset the gland appeared dark, friable, and necrotic. He therefore assumed that "gangrenous" pancreatitis was a later stage of the hemorrhagic form. What probably happens is that gangrene is present initially, though masked by the hemorrhage, and then becomes more visually prominent as the blood is altered or absorbed

Hemorrhage accounts for the color of the "prune juice" peritoneal fluid, frequently found in acute pancreatic necrosis, although the bulk of the fluid consists of peritoneal exudate which has arisen in response to irritation. Hemorrhage also is responsible for the ecchymosis that sometimes spontaneously appears in the flank (Turner's sign) or about the umbilicus (Cullen's sign) after the disease has been present several days Fallis (1937) explains these by stating that blood travels from the retroperitoneal position of the pancreas via the abdominal wall and finally localizes in one site. In a case of acute pancreatitis with umbilical discoloration Cox (1947) found the abdominal muscles infiltrated with old blood and a 2 ounce cavity containing some dark fluid that showed lipolytic activity.

The hemorrhagic nature of acute pancreatitis accounts for the marked anemia that may develop in severe cases, for large amounts of blood can escape into the retroperitoneal and peritoneal spaces.

use of the serum amylase test, popularized in this country by Elman, we have come to believe that edematous inflammation of the pancreas is more common than formerly supposed and that the majority of such cases resolve without mortality or complication. Elman (1933) felt that this lesion is a distinct pathologic entity and not a forerunner of necrosis, because the edema had often been observed several or more days after the onset of symptoms at a time when the acute process should have progressed to a maximum degree. He thought that this was a distinct clinical entity because it tends to subside without specific treatment. Popper et al (1948) have reached the same conclusion after showing that pancreatic edema, induced by ligature of the pancreatic ducts, can be transformed into pancreatic necrosis only if the gland is further damaged by temporary occlusion of the main pancreatic artery. If we assume that acute edema is present whenever transient acute upper abdominal pain is accompanied by an elevated serum amylase, then that lesion must be fairly common, a great deal more so than the more serious forms of acute pancreatitis

Hemorrhage

Hemorrhage in its most striking form disrupts the whole substance of the gland, converting it into a solid, boggy hematoma (pancreatic apoplexy). This is a sudden, catastrophic event and usually promptly fatal The bleeding presumably arises from an open pancreatic artery of medium caliber, but only occasionally can this be demonstrated Microscopically, there is nothing to be seen save red blood cells and disrupted parenchyma. Fitz considered this lesion a separate entity, but the more recent authors classify it under acute pancreatitis Somewhere, hidden in the hematoma, there is supposedly evidence of glandular necrosis, which preceded, and, by involving an artery, was responsible for the hemorrhage

Actually, hemorrhagic lesions in the pancreas are rarely massive and usually are accompanied by edematous swelling and spotty necrosis. Streaks of blood may lie beneath the peritoneum covering the gland, or blood may burrow into the parenchyma along the interlobular fissures, giving a "marbleized" appearance to the cut section, especially when the lobules are swollen and pale with edema Fresh hemorrhage may also be associated with areas of softening or with cysts, in which case necrosis of the tissue has occurred When large portions of the gland have been replaced by gray sludge or liquid matter, then necrosis has obviously antedated the recent escape of blood. Microscopically, the hemorrhage consists of red cells gathered in great numbers in the interstitial connective tissue. White cells may be more or less prominent as well Histologic evidence of necrosis, consisting of faded acinar cells or, in marked instances, of actual disintegration of architecture, is practically always visible. Usually the collections of red cells lie close to the areas of necrosis. Because hemorrhage and necrosis are so intimately connected, the two lesions are ordinarily discussed together as the twin signs of acute pancreatic necrosis, and although we discuss each separately, it must be remembered that one is hardly ever found without the other

Much interest has been centered on the nature and incidence of vascular lesions in acute pancreatitis. Smyth (1940) in a report of 40 necropsy cases of

impressed by the "specific vascular lesion" within the walls of the arteries, have presumed that the blood vessels are particularly susceptible to the injurious effect of trypsin and that hemorrhage precedes necrosis. The disruption of tissue caused by the active bleeding and the ischemia from impaired blood supply then produce necrosis of the gland This concept will not, however, account for isolated areas of necrosis, well removed from any hemorrhage.

Suppuration

Pus is characteristically not found in acute pancreatic necrosis nor in acute edematous pancreatitis. When present, bacterial contamination is considered to have occurred, and to distinguish that fact one can speak of suppurative pancreatitis. The pus may exist as multiple small abscesses in a swollen, red gland It may fill inflamed and dilated pancreatic ducts. It may take over a pseudocyst, turning it into a large abscess. Microscopically, large collections of polymorphonuclear cells, living and dead, are obvious. Red cells are not particularly evident, and areas of necrosis have usually been obscured by the cellular exudate.

Suppurative pancreatitis is considered less lethal than acute necrosis, probably because it represents a complication in those persons surviving necrosis. When multiple small abscesses are present, suggesting a hematogenous infection, hemorrhage and necrosis are infrequent companions, and thus mortality is lower.

Fat Necrosis

Although most frequently associated with lesions of the pancreas, fat necrosis can occur under other circumstances. Traumatic fat necrosis has been found in the female breast, and it also occasionally will develop in any fatty tissue that is subjected to trauma. In all instances the lesion probably appears as the result of the breakdown of neutral fat by a lipase. Necrosis or injury to the tissue allows the fat, released from cellular confines, to meet the enzyme, whether it be a liberated pancreatic enzyme or a local ferment arising from the regions of traumatic necrosis. Fatty acid and glycerol are formed. Glycerol, being water-soluble, is carried away, but the fatty acids may crystallize into irritating foreign bodies or may unite with calcium ions into insoluble soaps. Both products remain locally at the site of the injury. The calcium content of tissue subjected to fat necrosis is much higher than that of normal tissue (Edmondson and Berne).

Grossly the lesion appears as a firm, chalky, yellowish-white nodule or plaque, at times slightly raised above its surroundings, it varies in size from a scarcely visible speck to a structure several millimeters in diameter. When associated with pancreatic lesions, the nodule may be surrounded by a narrow zone of reddened tissue, denoting acute inflammation. It arises wherever fat cells are located and occasionally from serosal surfaces as well Since fat occurs in the interlobular connective tissue of the pancreas, fat necroses lie on the surface or within the gland The greatest numbers of them are usually found in and about the pancreatic lesion, but they often travel into the abdomen onto the mesentery and the omentum or backward into the retroperitoneal fat. In

NECROSIS

Necrosis is characterized by death of tissue. There is usually accompanying hemorrhage, as already emphasized Because acute pancreatitis in its severe form most strikingly shows necrosis, the name "acute pancreatic necrosis" is the most accurate description of that disease and is used in preference to "acute hemorrhagic pancreatitis", however, the first term does not exclude the presence of hemorrhage Gangrene or necrosis of the pancreas appears as soft, friable areas, ranging in color from yellowish-gray to black. Usually they are blood-tinged, but occasionally not. As the lesion grows older, the dead contents begin to liquefy, and in large lesions a cyst is formed which is lined by inflammatory tissue at the margin between necrotic and living gland Because of their inflammatory nature these collections of fluid are frequently called pseudocysts, to avoid the implication of neoplasm The fluid content of these pseudocysts tends to increase, perhaps because of the entrance of pancreatic secretion, and they may enlarge into big tumors that are easily felt.

Microscopically necrosis is easily recognized. In the mildest forms the cells retain their shape but are pale and no longer take nuclear stains. A notable feature of the lesion consists in the sharp demarcation between areas of necrosis and normal parenchyma without intervening change, and in the spotty almost indiscriminate distribution of the dead foci There may be no cellular exudate in and about the necrotic cells. In the larger fields of damage, disintegration of all structures, connective tissue, acini, and islet tissue alike, is apparent At the edge of such destruction amorphous debris and then a band of inflammatory cells, mostly polymorphonuclear, with an outer layer of red cells is often observed before unaffected parenchyma is seen Areas of necrosis may be replaced by scar tissue if the products of disintegration can be removed Small amounts can be absorbed by an inflammatory reaction ending in fibrosis, which remains as a permanent scar Large liquefactions cannot be naturally carried away, and the pancreas walls these off with a barrier of fibrous connective tissue in which a few round and plasma cells lie. If these cysts are drained surgically, the inflammatory walls collapse and fuse, leaving a pronounced scar.

Microscopically there may be signs of pancreatic duct obstruction consisting in dilated lumina with compressed, flattened mucosal linings. Rich and Duff say that they observed this change in 23 of 24 necropsies of cases of acute pancreatic necrosis Coagulated material may block the lumen of a small duct, often a metaplastic proliferation of the duct epithelium may do likewise Smyth (1940) found ductal metaplasia in only 13 of 40 cases, not a significantly higher incidence than found in normal subjects.

What has been said about the lethal and serious nature of pancreatic hemorrhage applies even more to pancreatic necrosis. Red cells can be carried away, but dead tissue leaves a permanent scar. Whether hemorrhage or gangrene comes first has never been settled, even though extensively argued. The views generally held (Opie and others) ascribe primary importance to necrosis of parenchyma, whether from the injurious effect of bile, pancreatic secretion, bacteria, or other agents, and further state that hemorrhage ensues when the advancing necrosis involves blood vessels. On the other hand, Rich and Duff,

have been identified clinically. Complete obstruction of the main pancreatic duct will, as we have seen, start a progressive atrophy of the parenchyma and a growth of scar tissue, without a preliminary stage of acute pancreatitis.

Scarring is a principal feature in the pathologic picture. Sclerosis leads to atrophy of the parenchyma, so that in extreme cases the pancreas becomes a small fibrous cord. Scarring causes obstruction of the ducts and results in dilatation of the drainage system. Scar tissue encloses and seals off cystic areas. In the early months or years of a chronic pancreatic lesion enlargement of the organ is usually found, presumably because the obstructed secretion distends the parenchyma (Martin and Canseco). Fibrous constriction in the head of the pancreas takes a more serious toll on the function of the gland than a lesion located in the tail, and it is more likely to propagate further scarring by virtue of being able to cut off glandular secretion.

Calcification

Calcification develops in a chronically diseased pancreas, as in the gallbladder. Some believe it may be the cause of chronic pancreatitis. When in the form of single or several large calculi lodged in the main pancreatic duct, the calcification is termed pancreatic lithiasis. Occasionally the process extends in a diffuse manner into many of the fine radicles of the duct system; in such a condition one can use the term diffuse calcification of the pancreas. Calcifications are usually located within the duct system; extraductal calcification may arise from old foci of fat necrosis.

The origin of pancreatic stones is not understood. They usually contain calcium and are radiopaque If removed surgically, they frequently re-form. Like stones elsewhere they prevent proper drainage and cause dilatation of the duct system and atrophy of the secreting parenchyma. Once present, they promote further damage to the gland.

Microscopically, the fibrosis respects no boundaries. The islands of Langerhans often survive for long periods in a sea of connective tissue, but gradually they dwindle in size Where former necrosis has wiped away all structures, the scar tissue contains no islands. Opie distinguished interlobular fibrosis from interacinar fibrosis. In the former, the connective tissue septa between lobules are thickened and encroach on the glandular parenchyma without invading it, thus encircling normal acini and islands. In interacinar fibrosis, the connective tissue makes its way into the center of lobules, engulfing all structures in its meshes. Opie noted that diabetes was more frequent in this latter type of fibrosis and was rare in the presence of interlobular fibrosis. Because of its similarity to hepatic portal cirrhosis, interlobular fibrosis is sometimes referred to as "pancreatic cirrhosis."

Certain other microscopic features may be noted. Clumps of hemosiderin bear reminder of old hemorrhage. Cellular exudate is not impressive, and consists of small numbers of round and plasma cells. The medium sized ducts frequently show dilatation and may be filled with homogeneous pink-staining material, indicative of static secretion. Occasionally pus cells are seen in the lumen. Calcified casts of the small ducts are easily identified when present.

severe cases of acute pancreatic necrosis the peritoneal cavity may be filled with these nodules, and occasionally they have been seen even in the subpleural and pericardial fat. Perry (1947) reported convincing evidence that the lipase responsible for spots of fat necrosis in acute pancreatitis travels by lymphatic pathways. Microscopically, in the center of the lesion the fat cells are dead with pale outlines, or they may be completely disintegrated. Blue-stained amorphous material is scattered about, and sometime one sees spicular crystals of fatty acid At the edge of the lesion leukocytes and beyond them red cells may be collected, and the neighboring small vessels often are congested The inflammatory response seems to be secondary to the initial necrosis. Later, foreign body giant cells group themselves about the crystals of fatty acid.

Once established, fat necroses disappear very slowly, and may be seen months after the initial injury If they become calcified, as they frequently do, they remain as permanent lesions Pancreatic fat necrosis may occur alone in the absence of any other lesion It may accompany any of the forms of acute pancreatitis, though less frequently the suppurative variety, and in severe cases of hemorrhagic necrosis it is almost always present. In the absence of other lesions fat necrosis is not serious except as a sign that the pancreas has been disturbed Mild trauma or ligature often produce small local nodules that have no significance for the development of an acute pancreatic necrosis. The chief importance of fat necrosis is that it allows the surgeon to diagnose the presence of pancreatic disease.

Cause of Death in Acute Pancreatitis

Formerly there was much discussion as to what made this acute disease so deadly The shock, prostration, and anemia which Fitz described are probably in part related to dehydration and blood loss. The liberal use of blood and intravenous fluids practiced today has made these factors less prominent in fatal cases When they have been eliminated, one still can postulate the idea of a lethal toxin being elaborated by the necrotic tissue. Formerly the peritoneal exudate in acute pancreatitis was thought to be highly toxic, even long after Whipple and Goodpasture (1913) showed that it was not, and surgeons made earnest effort to sponge out all such fluid from the peritoneal cavity (Schmieden and Sebening) Dragstedt et al. (1934) after a number of careful experiments concluded that sterile, autolyzing pancreas was harmless, whereas the presence of anaerobic, gram-positive organisms similar to *Cl welchii* in the necrotic pancreas was highly lethal to dogs They believed that such bacteria elaborated poisonous toxins when allowed to grow in dead tissue. Although this explanation may be questioned, there has been no experimental work to suggest a better answer The problem still awaits complete solution.

Chronic Pancreatitis

The origin of the changes noted in the chronically diseased pancreas is even less well understood than those occurring in the acute disease. Presumably all chronic pancreatitis has been preceded by an acute lesion at one time or other, although in many instances the acute episode was too mild and transient to

acute pancreatitis in 15 per cent of 89 soldiers suffering from mumps Patients with pancreatitis recovered after several days of such abdominal symptoms as pain, nausea, and vomiting. (4) Miscellaneous factors that may predispose a patient to the development of acute pancreatitis include: peptic ulcer which perforates into the head of the pancreas; operative procedures on or about the pancreas; toxic chemicals, notably arsenic when administered intravenously; prolonged debilitating diseases, such as typhoid fever.

Previous Abdominal Symptoms

At least half of the patients who enter a hospital with an attack of acute pancreatitis have had abdominal symptoms during the preceding months or years. These symptoms, if mild, consist of transient, ill-defined dyspepsia and vague indigestion, but in many instances actual attacks of abdominal pain have occurred similar to those of acute pancreatitis and presumably caused by mild edema of the gland These attacks are either not severe enough to send the patient to a physician or are misdiagnosed. Individuals who have had no previous gastrointestinal or abdominal complaints are not likely to develop a severe case of acute pancreatitis without warning.

Symptoms of Acute Pancreatitis

Clinically acute pancreatitis begins in the upper abdomen with a relatively sudden pain which arises in the midepigastrium, occasionally in the right upper quadrant, and radiates to the back or to the left flank. When it originates in the region of the gallbladder, the pain primarily suggests cholecystitis and may mislead the physician, but if it spreads to the left lumbar area and to the left flank, this symptom points to pancreatitis and, in particular, to irritation within the lesser peritoneal cavity. Less commonly it radiates transversely in the epigastrium or becomes generalized in distribution. Pain is the most prominent single symptom of the disease and only rarely is absent The severity of pain is a rough index of the degree of pancreatic damage. In mild cases of edema the pain may be no more than slight epigastric distress, and as the pathologic lesion progresses, the pain increases until it attains excruciating proportions in the event of marked edema or necrosis of the gland. Characteristically, the pain is steady, unrelenting, and uninfluenced by vomiting. Even morphine, which eases the pangs of biliary colic, affords only slight relief. At the onset of the usual case of acute pancreatitis the character of pain unfortunately does not lead to a specific diagnosis between the various acute afflictions of the upper abdomen

Nausea and vomiting promptly follow the pain. Although in the mildest instances only nausea is noted, usually vomiting of a reflex nature is conspicuous and persistent. Continuous gagging, retching or vomiting of bile despite an empty stomach dehydrate and exhaust the patient.

Fever is mild or absent, and chills do not occur Much emphasis has in the past been placed on the dramatic development of shock as an indication of acute pancreatitis (for instance, Fitz's description of a patient who died in 30 minutes). In those occasional instances when shock is found within the first 24 hours of the disease, the pancreas is always severely damaged by massive hemorrhage or necrosis, and death follows promptly The large majority of patients do not

CLINICAL FEATURES OF ACUTE PANCREATITIS

Historical Review; Definition

According to Fitz (1889), Classen in 1842 was the first to establish the clinical entity of acute pancreatitis Fitz in his own study differentiated three types of the disease: hemorrhagic, gangrenous, and suppurative. More recent observations, particularly *those of Zoepffel (1922) and Elman (1933, 1942), have* emphasized a milder form of acute pancreatitis, acute edematous or acute interstitial pancreatitis.

Acute pancreatitis, as a clinical entity, includes all the pathologic varieties of acute pancreatic inflammation It may be subdivided into three categories: (1) Acute edematous (interstitial) pancreatitis refers to the benign form in which the chief pancreatic lesion is edema. (2) Acute pancreatic necrosis and acute hemorrhagic pancreatitis are generally used interchangeably to denote pancreatitis characterized by hemorrhage and necrosis. (3) Acute suppurative pancreatitis implies the presence of purulent exudate within the pancreas. Since the various pathologic subdivisions of acute pancreatitis cannot be distinguished clinically at the onset of the disease, physicians are justified in retaining the general term acute pancreatitis until the subsequent course of the disease clarifies its pathologic nature Wherever possible, the specific terminology should be used

In the general clinical discussion of acute pancreatitis that follows the reader will note that the disease begins with a sequence of a few nonspecific symptoms and findings. As the illness progresses in the course of several days, it assumes more specific characteristics which inform the physician about the nature of the pancreatitis and the prognosis in the individual case

Age and Sex Incidence

Acute pancreatitis is predominantly a disease of middle age, but it may affect both children and elderly adults Females are afflicted more frequently than males No reason can be given for the difference in sex incidence other than that which points to the greater frequency of gallstones in women.

Precipitating Factors

Several factors have been observed which, although not the direct cause of pancreatitis, precede and may contribute to the onset of the disease (1) The typical patient with acute pancreatitis is traditionally obese, but probably more significant than corpulence is the frequent history of the ingestion of a large meal shortly before the onset of abdominal pain Perhaps corpulent individuals are susceptible to the disease because they tend to overindulge their appetites. (2) Alcoholism is prominently associated with pancreatitis, especially in cases seen at large city hospitals Of 307 cases reported by Paxton and Payne (1948) 18 *per cent* were either intoxicated or recovering from a recent alcoholic spree on admission. (3) Mumps, or epidemic parotitis, may be complicated by the development of acute edematous pancreatitis in a small but definite percentage of patients. With the help of the serum amylase test, Zelman (1944) diagnosed

colon prior to the onset of paralytic ileus. In a general way, therefore, the overall absence of striking abdominal findings distinguishes acute pancreatitis in its earlier stages from other upper abdominal emergencies.

After the first day or two of a moderately severe illness, or promptly in extreme cases, examination of the abdomen reveals signs of greater significance. Epigastric tenderness is unequivocal and is associated with well defined muscular spasm in the upper abdomen. The irritation which arises from a serious pancreatic lesion, whether edematous, necrotic, or suppurative, produces both a reflex paralysis of the bowel and a chemical peritonitis. The ileus, most prominent in the jejunum, is manifested by tympanitic swelling of the upper abdomen, by absent or scarcely audible peristalsis, and by troublesome constipation. A general peritoneal effusion, colored a typical "prune juice" shade by hemolyzed blood, produces diffuse abdominal tenderness and shifting dullness in the flanks. Clotted blood does not move about in the peritoneal cavity, and, when collected in the lumbar gutter, may cause only an increased dullness and tenderness in the flank. An effusion within the lesser peritoneal cavity is almost impossible to detect in its early stages by physical examination, but operative and postmortem examinations have established that it occurs with great frequency in acute pancreatitis. The effusion can be noted mainly by its indirect effect on neighboring organs, notably a displacement of the stomach upward and forward, an elevation of the left diaphragm, and a pleural effusion at the left lung base. If, as usually happens, the foramen of Winslow becomes sealed off by inflammatory exudate within the lesser cavity, in the course of several days the trapped fluid distends the cavity to such an extent that a tender mass can be felt in the epigastrium.

Much clinical emphasis has been placed on the appearance of ecchymosis about the umbilicus (Cullen's sign) or in the flanks, particularly on the left (Turner's sign), since these discolorations are almost pathognomonic of acute pancreatitis. Cullen's sign may, however, as originally described, accompany a ruptured tubal pregnancy. Both of these signs in pancreatitis depend on the extravasation of blood into the retroperitoneal tissues from a marked hemorrhage in the pancreas. The blood dissects forward to the flanks and may proceed to the umbilicus where it collects because of a peculiar arrangement of the fascia These signs are rarely observed and, if present, indicate severe hemorrhagic pancreatitis Their usefulness in establishing a diagnosis is further diminished by their relatively late appearance in the illness, generally from the third to the tenth day Good illumination may be needed to recognize the ecchymotic discoloration, since it is not intense.

RELATED SYMPTOMS AND PHYSICAL FINDINGS

Patients with acute pancreatitis often present some misleading symptoms and signs which may result from secondary effects of the primary disease but which in other instances cannot be logically explained.

(1) Gastro-intestinal hemorrhage, in the form of bloody vomitus or bloody diarrhea, may be seen in severe instances of pancreatic hemorrhage and necrosis. In some of these patients postmortem examination has revealed acute ulcerations in the stomach, duodenum, and colon. Although the cause of such ulcerations is not evident, it has been suggested that if alkaline pancreatic juice no

lapse into shock unless dehydration and uncontrolled pain cause a fall in blood pressure several days after the onset of the disease.

If the patient is not seen until the second or third day of the illness, further symptoms may develop to help delineate the disease. In the average mild case the pain begins to subside after 48 hours, and the vomiting ceases. On the other hand, pain that remains unabated or increases indicates the more serious pancreatic lesions. In the persistent cases paralytic ileus develops on about the third day and is accompanied by constipation and slight bloating of the epigastrium. As the ileus becomes more pronounced, the vomitus increases in amounts and may assume the appearance of intestinal contents.

PHYSICAL FINDINGS

In contrast to the alarming nature of the symptoms the physical examination reveals few abnormalities The patient is rarely in shock, although he often exhibits an anxious weariness, common with any severe abdominal pain. When present, shock is usually severe, and the patient appears moribund. A peculiar ashy cyanosis of the extremities and face with pallor about the lips, marked hypotension, a rapid, weak pulse, and semi-coma may be observed but are not diagnostic of acute pancreatitis in the absence of further information. Patients in this condition rarely survive more than a few hours, and unless the serum amylase is determined the diagnosis is made only at necropsy. On the other hand, subclinical shock, suggested by thirst, pallor, and restlessness, is present in most of the moderately severe cases. Although the blood pressure remains near normal limits and the pulse does not become exceedingly fast, impending collapse can be detected by signs of dehydration Sudden shock early in the disease generally signifies massive hemorrhage from the pancreas into the abdomen or retroperitoneal tissues The gradual appearance of shock after a day or two of illness can probably be explained in two ways. The more obvious cause consists in the depletion of blood volume by bleeding from the pancreas, by persistent vomiting, and by the development of large collections of fluid exudate in the greater and lesser peritoneal cavities. The total loss of fluid by these various routes may amount to several or more liters in the course of even one day In addition to a depletion of blood volume, shock may result in an ill-defined manner from toxic products which are liberated by the damaged pancreas, especially in instances of marked necrosis.

In the moderately ill patient the temperature is normal or only mildly elevated, while the pulse is increased to about 100 With impending or actual shock the temperature falls to between 35 to 36 5°C Significant physical findings, if available, center about the upper abdomen Usually the epigastrium shows moderate *tenderness* in a general area corresponding to the site of the pain, but occasionally no definite tenderness is elicited Tenderness in the left flank or lumbar area may accompany lesions in the tail of the pancreas or in the lesser peritoneal cavity. Spasm of the abdominal muscles is not as a rule present in mild cases, a helpful negative finding, although voluntary guarding in the epigastrium commonly occurs. In the early typical case peristalsis is normal or slightly hypoactive to auscultation and the abdomen is not distended with fluid or gas. Diarrheal stools, occurring at this point of the illness, indicate a reflex irritation of the

available at the present time which will unequivocally make this diagnosis. The various clinical laboratory features of acute pancreatitis are: (1) elevated blood amylase, (2) elevated urinary amylase; (3) elevated blood sugar and sugar in the urine, (4) low blood calcium; (5) roentgenologic findings; (6) electrocardiographic changes.

Blood Serum Amylase. In 1908 Wohlgemuth developed an iodometric method * for the determination of the blood serum amylase on the basis of his original urinary diastase test. The clinical application of this test was not widely recognized until recently because it had not been performed early in the course of the disease when the blood amylase is elevated. In this country Somogyi in 1938 developed a saccharogenic method** for the determination of blood serum amylase which has been widely used This test is the most important single diagnostic tool. When all laboratory factors are well controlled, the test is

* The Wohlgemuth *iodine* test, still used extensively in Europe, depends on measuring the loss of starch substrate by observing the blue color formed by the union of iodine and starch. Briefly, the technic consists of placing a known amount of starch substrate in a series of test tubes and then adding serum or plasma in quantities that serially diminish by 0 1 cc The starch-serum mixture is incubated at 37°C for 45 minutes, after which enzyme activity is stopped by adding cold water to the tubes Iodine is used as an indicator, and the first tube in which the blue color of the iodine starch complex is lost is taken as an end point. Amylase units are then expressed as the volume of serum which is required to change 1 cc. of starch from a blue to a purplish color, and they are usually stated as units per cc. of serum Because of the dilution factor in succeeding tubes, Wohlgemuth values for amylase generally run in geometric progression, and the shift of end point from one tube to the next causes wide variation in values. The test is quick and simple, despite its relative inaccuracy

A promising modification of the iodometric principle is that of Huggins and Russell (1948), who use a colorimeter to measure the change in the blue color of a starch-iodine complex. Incubation of starch, serum, and buffer is carried out for an hour, after which iodine and fluoride ion are added The fluoride stops digestion The solution is read in a colorimeter with a 660 mμ filter, and comparison of the reading to that of a mixture not incubated gives an expression of the per cent loss of starch The result, stated as units, indicates that one unit equals the amount of enzyme which hydrolyzes 1 mg of starch in one hour at 37°C. and at pH 7 0. Normal values range from 9 to 35 units.

** The *saccharogenic* methods determine the amount of sugar produced by the serum amylase following digestion of a known amount of starch Alkaline copper reagents are reduced by the sugar so liberated, and the degree of reduction is determined colorimetrically. Somogyi (1938) has popularized this method, and his procedure is in common use in the United States Serum, substrate, and buffer are incubated at a known temperature for a known period of time (usually 30 minutes) At the end of incubation digestion is stopped by precipitating the protein, and the filtrate is tested for sugar by measuring the reduction of a copper reagent Amylase activity in units is expressed as milligrams of reducing sugar formed as glucose by 100 cc of serum Control determinations must be run simultaneously and their value subtracted from that of the test mixture Normal values with Somogyi's method range from 80 to 180 units, with an average of about 120

Myers et al (1944) advocate a variant of this procedure, by measuring the quantity of maltose formed as an end product, using picric acid as the reagent to be reduced Their normal values, in milligrams of reducing sugar formed by 100 cc of serum, average 182 mg. per cent.

Viscosimetric methods measure the decrease in the viscosity of a starch solution as it is being hydrolyzed by a serum amylase Incubated digestion mixtures are examined in an Ostwald viscosimeter at various intervals until viscosity is reduced by 20 per cent. Though simple, the test has certain objections, chief of which is that change in viscosity does not bear a linear relation to time of incubation.

longer flows into the duodenum, the duodenal secretions become strongly acid, and consequently, when regurgitated into the pylorus, favor the development of peptic ulcers in the stomach or duodenum

(2) Jaundice in the absence of gallstones has occasionally been reported in acute pancreatitis, but not nearly as frequently as in chronic pancreatitis. Because the common bile duct in its terminal portion lies on or is surrounded by the head of the pancreas, common duct obstruction is readily caused by edematous swelling of the gland, but since edematous pancreatitis appears abruptly and tends to subside within several days, the obstruction is transient, and clinical jaundice does not usually develop Determinations of the serum bilirubin during the acute phase of the disease will probably reveal a surprisingly large number of cases with laboratory evidence of obstructive jaundice in the absence of clinical signs.

(3) The presence of hypertension in patients with acute pancreatitis has recently been stressed by Paxton and Payne, who observed elevated blood pressures in 20 per cent of 307 cases. These authors pointed out that the average age of the total series (41 years for males and 49 years for females) was younger than the period of life in which hypertension is common Although this phenomenon is unexplained, it may be recalled that Rich and Duff described in acute pancreatitis a vascular lesion of the pancreatic vessels which resembled the arterial lesion in renal arteriosclerosis associated with hypertension

Having obtained a history and performed a physical examination the physician may strongly suspect acute pancreatitis, but he cannot make a positive diagnosis early in the disease without help from the laboratory. On the other hand, the wise diagnostician will acquire a thorough knowledge of the aspects of the case in question, before resorting to laboratory tests.

Laboratory Features

The results of laboratory tests in a case of acute pancreatitis may be divided into findings which are nonspecific and those which are characteristic A brief discussion of the routine tests will precede the description of the more diagnostic features.

In the early stages of the illness, when dehydration is common, the *blood* reveals a normal or high number of red cells associated with normal or elevated values of hemoglobin and hematocrit Once dehydration has been corrected, mild anemia may appear, and a low red cell count indicates extensive hemorrhage from the pancreas By following the level of red blood cells the physician is aided in deciding when to use blood transfusions and what the prognosis may be Moderate *leukocytosis* (10,000 to 15,000) usually is found Necrosis may elevate the white blood cell count to 25,000. If the level of leukocytes in the course of acute pancreatitis suddenly rises, the onset of suppuration in the gland must be suspected The *urine* is usually concentrated, reflecting dehydration, and in moderately severe cases albuminuria is common, accompanied at times by granular casts and an occasional red cell Glycosuria is also frequent and is further discussed with the characteristic laboratory findings.

The aid of the clinical laboratory is necessary to make a positive diagnosis of acute pancreatitis It must be emphatically stated that no laboratory tests are

of amylase is starch. Starch solutions defy exact chemical analysis and do not conform to set patterns. Thus, there is great uncertainty whether the starch used for one test will be identical with that used in another.

Determination of Serum Lipase: As in the case of amylase, one of the chief obstacles to a prompt, simple test of serum lipase has been the difficulty in finding a suitable substrate. The most widely used method, that of Cherry and Crandall (1932), uses olive oil as a substrate and requires incubation for 24 hours, a serious clinical disadvantage. After incubation the mixture is titrated with sodium hydroxide (phenolphthalein indicator) to detect the amount of acid formed by the breakdown of fat. Results are expressed as the number of cubic centimeters of 1/20 normal sodium hydroxide required to neutralize the acid formed by the action of 100 cc. of serum. Values above 1.5 cc. are considered abnormally high.

A simpler, more uniform substrate, tributyrin, has been proposed, which will permit incubation for one hour and at the same time yield reliable values (Goldstein and Roe, 1943). Popper (1948) preferred the serum lipase test to the amylase determination, on the grounds that it is a more delicate indication of pancreatic dysfunction, especially in obstruction of the pancreatic ducts.

Duodenal Enzyme Tests: Since Agren and Lagerlof in 1936 described their method of collecting pancreatic secretion from the duodenum after stimulation of the gland with secretin, a number of authors, including Diamond and Siegel (1940), have reported extensive surveys which record the amounts and concentrations of pancreatic enzymes released into the duodenum under various conditions. A rubber tube with two lumina is passed into the duodenum via the mouth and is constructed so that when the longer end rests in the duodenum the shorter one lies in the stomach. The lumen ending in the stomach is designed to remove gastric secretion, thereby preventing dilution of duodenal contents The fluid aspirated from the duodenum is presumably pancreatic secretion, after the amount of bile present has been calculated and subtracted. The duodenal aspirate is collected continuously until a base line of fasting secretion has been reached, usually within one hour, and then secretin is administered intravenously to produce a copious flow of pancreatic juice. Samples are then collected for measured intervals throughout a period of an hour or more. These labeled samples are then promptly examined for volume, bicarbonate content, and enzyme content. The procedure is cumbersome and requires constant attention during the collection of samples, it can hardly be used on the very ill patient because of the inconvenience of passing a tube into the duodenum. Lagerlof (1942) believed that the important practical results consist of the behavior of volume, total bicarbonate ion, and total amylase content.

If these values fall below normal, one can assume that an insufficient amount of pancreatic juice is reaching the duodenum. Either atrophy of the secretory parenchyma or obstruction of the pancreatic ducts by tumor, inflammation, or stone may cause that diminished secretion. No specific pathognomonic features rest in the figures of a duodenal analysis beyond a general indication of atrophy or obstruction This knowledge may be helpful in chronic, obscure ailments within the abdomen, but usually the diagnosis of pancreatic disease can be

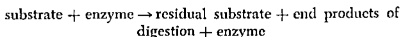
invaluable except in the instance of borderline values and except for the inherently variable behavior of the pancreatic amylase in a given patient with pancreatitis. Elevation of the blood serum amylase is seen most frequently with parotitis and acute pancreatitis It is now an established fact that if the blood serum amylase test is done within the first two or three days of an acute illness, a low or normal reading is of considerable value in eliminating the possibility of acute pancreatitis. In all cases of suspected or actual acute pancreatic disease this test should be repeated frequently during the first 72 hours and at daily intervals thereafter.

McCorkle and Goldman have described six variations in the curve which expresses the behavior of the serum amylase level in acute pancreatitis: (1) sharp rise and fall to normal, (2) sharp rise and fall to subnormal; (3) fluctuations following the clinical subsidence of acute pancreatitis, (4) sustained high levels, (5) secondary elevations; (6) slight increases, but these observers have pointed out the limitations and spontaneous variations of the blood serum amylase test in relationship to its diagnostic value. Of all available diagnostic tests the blood serum amylase determination affords the most reliable aid

Diagnostic Enzyme Tests. A certain amount of amylase and lipase, similar and perhaps identical to the enzymes manufactured in the pancreas, can be found in normal blood The urine and duodenal contents also contain measurable amounts of both enzymes. During various diseases of the pancreas, especially acute pancreatitis, the amount of enzymes in the blood stream increases Accurate measurement of this increase would be a valuable diagnostic tool.

At present, the scale of biologic activity is the only practical yardstick for comparing concentrations and strength of enzymes. In order to set up standard, repeatable tests for a particular enzyme one must control among others the following highly variable factors: (1) pH at which the enzyme acts, (2) temperature at which the enzyme acts, (3) substrate which is digested by the enzyme, (4) time during which the enzyme acts. These and many other conditions influence the speed and amount of enzyme activity. A variation in any one factor will alter the end result of a test.

The following simplified formula expresses the process of enzymatic digestion.



substrate + enzyme → residual substrate + end products of digestion + enzyme

Clinical tests depend (1) on a simple measurement of the amount of end products formed; (2) upon the diminution in the amount of substrate after digestion, or (3) upon changes in the physical characteristics of the mixture of residual substrate, end products, and enzyme. No test, therefore, is an expression of the actual amount of enzyme present but is merely an attempt to express the degree of its activity.

Determination of Serum Amylase. The activity of serum amylase has been studied intensively since Wohlgemuth (1908) described his method of determination. Because of the difficulty in controlling the many variables that govern enzyme activity, no one method of expressing the serum amylase is completely satisfactory. One of the most elusive variables is the substrate, which in the case

stomach and increased size of the duodenal loop may be seen in cases of pancreatic enlargement or pseudocysts of the pancreas. A tender swelling of the pancreas may be noted on palpation at fluoroscopic examination. Roentgenographic findings are not pathognomonic of acute pancreatitis, though they may aid in diagnosis. Roentgenologic examination is of particular value in establishing a differential diagnosis of perforated ulcer.

Electrocardiography. Recently several observers, notably Gottesmann et al. (1943), have indicated a series of electrocardiographic changes which they regard as specific for acute pancreatitis. Although a certain percentage of patients will show such changes, there is nothing diagnostic in the pattern. In our own clinical study we were unable to find any consistent electrocardiographic pattern diagnostic of acute pancreatitis, nor could we find any correlation of changes in an experimental study. Two plausible explanations for such electrocardiographic changes may be suggested: (1) a low calcium level; (2) a disturbance of the vagal impulses via the celiac plexus, or a combination of both of these factors.

Course and Complications

Acute pancreatitis in its early stages cannot be clinically differentiated into pathologic types as previously stressed, but as the disease progresses, certain features appear which tend to identify the particular form.

(1) Acute edematous (interstitial) pancreatitis is present in two-thirds to three-quarters, and perhaps more, of all cases with acute pancreatitis. In mild instances of edematous pancreatitis recovery usually begins two to three days after the onset of the illness. Pain disappears; appetite returns; and soreness gradually leaves the epigastrium. Within a week or less the patient is ready to resume a normal life. Even in a moderately severe case the course rarely lasts more than two weeks. In severe fatal cases death as a rule occurs early in the disease, within the first four days. Transient jaundice is more likely to appear in acute edema of the head of the pancreas than in other acute lesions of the pancreas Fat necroses may be widespread in connection with edematous pancreatitis, but cause few if any symptoms Paxton and Payne reported severe coronary pain in 3 cases of acute pancreatitis with fat necroses in the left pleura and pericardium.

(2) Acute pancreatic necrosis or acute hemorrhagic pancreatitis is found in one-third to less than one-quarter of cases with acute pancreatitis. Symptoms are usually pronounced but may be deceivingly mild. If a patient fails to improve after several days, and signs of intra-abdominal inflammation persist, pancreatic necrosis or hemorrhage is probably responsible for delayed recovery. In fatal cases death usually occurs before the fourth day, but at times it may be postponed for two to three weeks until precipitated by secondary infection or pneumonia Collections of inflammatory fluid and secretion within the pancreas *(pseudocyst)* frequently result three to four weeks following the attacks of pancreatic necrosis, and occasionally earlier. They are first noticed in the form of a slightly tender, epigastric mass, in the midline or on the left, in patients who may be entirely asymptomatic. Usually the mass causes upper abdominal distress and may be accompanied by mild low grade fever and leukocytosis. Since the semiliquid contents of the cyst are sterile, consisting of autolyzed pancreatic

made from other simpler methods This analysis will not differentiate between carcinoma and inflammation of the head of the pancreas.

Urinary Amylase A urinary amylase test was developed by Wohlgemuth to measure the amylolytic enzyme secreted by the kidney and is determined by a method of starch hydrolysis Originally he used the test as an index of renal inadequacy but noted that in pancreatitis the urinary amylase was elevated. The test consumes too much time to be of real diagnostic help in acute pancreatitis, hence the blood serum amylase test is superior In renal disease retention of amylase in the blood is readily noted if both serum and urinary amylase determinations are made.

The urinary diastase usually becomes elevated 12 to 24 hours later than elevation of the blood serum amylase. It usually remains elevated longer, however, these features are not constant

Determination of Urinary Amylase. Amylase in the urine represents the enzyme which has been cleared from the blood stream by the kidney. When the kidney is functioning properly, the activity of urinary amylase parallels that of the serum amylase in the same person, but when kidney function is reduced by nephritis or dehydration, the values of urinary amylase vary widely from those occurring in the serum Furthermore, in normal persons the concentration of urinary amylase varies from one hour of the day to another, according to Dozzi (1940) In general, therefore, serum amylase tests are more reliable. Any of the methods used to determine serum amylase can be adapted to the measurement of urinary amylase A saccharogenic method is probably the most accurate except in the presence of marked glycosuria

Hyperglycemia and Glycosuria Elevation of the blood sugar in some patients with acute pancreatitis has been noted by many observers. Hyperglycemia has been noted in many cases without previous evidence or history of diabetes mellitus, as has been mentioned Although more thorough clinical observations must be made before positive conclusions can be drawn, in those patients with hyperglycemia the blood sugar levels should be checked by periodic glucose tolerance curves Shumacker (1940) noted that in severe acute pancreatitis 2 per cent developed diabetes during the disease, and 3 to 10 per cent in the immediate follow-up period.

Correlation of glycosuria with hyperglycemia in patients with acute pancreatitis has also been noted Shumacker reported the presence of sugar in the urine in 11 per cent of patients with acute pancreatitis.

Blood Calcium. Edmondson and Berne and others have reported a depression of blood calcium in acute pancreatitis The exact mechanism for this disturbance is not yet known It is believed to be due to utilization of the ionizable calcium in areas of fat necrosis The blood calcium may fall from a normal level of 10 mg. per cent to as low as 5.4 mg per cent Trevor and Brown (1944) reported one patient with acute hemorrhagic pancreatitis and associated fat necrosis in whom clinical tetany developed on the third day of illness

Roentgenography In the later stages of acute pancreatitis roentgenologic films of the abdomen may reveal a segmental ileus involving a portion of the gastrointestinal tract, usually the jejunum In a series of 307 cases reported by Paxton and Payne, 68 per cent revealed a segmental type of ileus. Displacement of the

there are a number of upper abdominal and even lower abdominal surgical conditions of the acute variety which make the clinical diagnosis of acute pancreatitis difficult. Some of the more common are acute cholecystitis, perforated peptic ulcer, acute intestinal obstruction, acute appendicitis, and mesenteric thrombosis. On the other hand, there are a few medical conditions which also simulate the classical picture of acute pancreatitis and which will require consideration before a differential diagnosis can be made. Some of these conditions are acute coronary disease, biliary colic, pneumonia, dissecting aneurysm of the upper abdominal aorta, and on occasions tabetic crisis. Because of the difficulty encountered in making the correct diagnosis on a clinical basis, we believe it worth while to repeat the salient points of the differential diagnosis of these various conditions.

Acute Cholecystitis

Frequently the pain produced by acute pancreatitis is indistinguishable from that of acute cholecystitis, but is usually confined to the midline in the epigastrium or to the left upper quadrant. Pain in acute cholecystitis is usually in the right upper quadrant. It may radiate around the back to the tip of the scapula or between both scapulae. In acute cholecystitis deep respiration may be painful, and with the examiner's thumb or fingers in the right upper quadrant, the area may be excruciatingly tender on deep respiration This is known as *Murphy's sign.* In acute cholecystitis a patient may reveal tenderness and muscle spasm localized in the right upper quadrant, but in spite of the spasm the gallbladder may be palpated as a tender mass In many instances emergency roentgenography may reveal stones in the gallbladder region, which are helpful in directing attention to this organ and away from the pancreas. Fever and chills tend to indicate cholecystitis but are not characteristic of acute pancreatitis.

Perforated Peptic Ulcer

A free perforation of a peptic ulcer may more nearly simulate acute pancreatitis than perhaps any other acute upper abdominal condition. In perforation of a peptic ulcer there is more generalized abdominal rigidity than is seen in acute pancreatitis. In the majority of cases the entire abdomen is said to be "boardlike," whereas in acute pancreatitis the pain and muscle spasm are usually confined to the epigastric region Usually in a perforated peptic ulcer there is a history of dyspepsia relieved temporarily by food or alkali, although occasionally the perforation is the patient's first intimation of disease. Although one may suspect a perforated peptic ulcer, occasionally the history and the physical findings are so parallel to that of acute pancreatitis that a clinical differential diagnosis cannot be made. In such an instance roentgenograms may prove to be helpful Films taken with the patient in an upright position or in the right lateral *decubitus* position may clearly demonstrate the presence of a pneumoperitoneum These roentgenologic findings would immediately suggest the rupture of a hollow viscus, most likely a perforated peptic ulcer.

Acute Intestinal Obstruction

Acute intestinal obstruction, particularly in the upper abdomen, may closely simulate the picture of acute pancreatitis. Severe intermittent pain of a cramp-

tissue, old blood, and pancreatic secretion, there may be little or no systemic reaction to the growth of the cyst When bacteria become established in the inflammatory masses, the organisms evoke a purulent exudate and change the pseudocyst into an *abscess* Pseudocysts often rupture into the lesser peritoneal cavity, or may dissect ventrally between the leaves of transverse mesocolon, and occasionally discharge their contents into the colon or adherent loops of small intestine. Although small cysts may be resolved spontaneously, those which are palpable externally usually require some form of surgical drainage. *Diabetes*, as shown by glycosuria and hyperglycemia, may appear early in the course of severe pancreatic necrosis and disappear as recovery takes place. On the other hand, as reparative fibrosis constricts the remaining intact gland, the islands of Langerhans may be diminished in amount, even below the number which functioned during the height of the disease; thus diabetes may make its appearance after the acute process has fully subsided. According to Shumacker (1940), diabetic coma may be seen in the course of acute pancreatic necrosis *Thrombosis* of the splenic and portal veins may be caused by severe pancreatic damage.

A certain proportion, perhaps a third or more, of patients who survive the first attack of acute pancreatitis, either edematous or hemorrhagic and necrotic, will endure at least one additional bout of the same disease If periodic attacks continue, the pancreas becomes *chronically inflamed* and ultimately becomes atrophied throughout. At present, there seems to be no way of predicting which patient with acute pancreatitis is destined to develop a chronic and disabling form of the disease; hence every effort should be made to prevent recurrences of this unfortunate illness.

(3) Suppurative pancreatitis may occasionally result from a primary bacterial invasion of the gland, such as multiple metastatic abscesses transmitted by the blood stream or lymphatic vessels, or as suppuration extending directly from a neighboring purulent focus. In these instances, the purulent inflammation within the pancreas is usually only a manifestation of a generalized infection, and symptoms of pancreatitis, such as epigastric pain and vomiting, are masked by those of marked systemic toxicity.

Acute suppurative pancreatitis commonly refers to the supervention of bacterial organisms on the lesions of pancreatic necrosis and, occasionally, edema As a secondary event, suppuration may begin a day or two following the onset of the disease, but usually is first seen after five to seven days or more. Unless a febrile episode occurs in the course of convalescence, no clear-cut signs mark the beginning of suppuration, which can be identified mainly by an abnormal rise in fever and increased leukocytosis The large pseudocysts of pancreatic necrosis unfortunately tend to become infected, and under such circumstances they create the serious problem posed by an intra-abdominal abscess With virulent infection the subsequent course is stormy and frequently fatal, whereas a mild infection can often be effectively handled by the bodily defenses.

DIFFERENTIAL DIAGNOSIS OF PANCREATITIS

It becomes obvious that the differential diagnosis of acute pancreatitis is a most important problem to the clinician. Time is important since unnecessary delay may, for a specific surgical lesion, invite disastrous results. In this regard

tinal obstruction. The onset is not so sudden as in acute pancreatitis. Most of the symptoms and signs of acute mesenteric thrombosis simulate acute pancreatitis so perfectly that the differential diagnosis is difficult. A mild bloody diarrhea is not uncommon in acute mesenteric thrombosis, however, and may be an important diagnostic sign in this condition. In mesenteric thrombosis of the colon intensity of shock is usually out of all proportion to the abdominal findings and hence may suggest this syndrome. Moreover, diffuse abdominal tenderness and muscle spasm are common in mesenteric thrombosis; whereas in acute pancreatitis pain is localized for the most part in the epigastrium and the left upper quadrant.

Renal Colic

Although in the majority of cases of renal colic a differential diagnosis from pancreatitis would not be too difficult, it is possible that a stone in the left ureter would create difficulty in making a positive diagnosis. The pain of renal colic is knife-like and usually radiates toward the thigh or genitalia. When the stone enters the ureter the pain can be so excruciating as to produce nausea and vomiting and spasm of the abdominal wall musculature, and may even cause collapse of the patient, a phenomenon referred to as *Dietl's crisis* In general, observation of the patient and examination of the urine with findings of hematuria will establish the differential diagnosis.

Biliary Colic and Common Duct Stone

Biliary colic in an extreme degree may simulate acute pancreatitis. In biliary colic, which is really acute cholecystic obstruction, the origin of the pain is not certain, but apparently it is associated with such factors as spasm or contraction of the gallbladder, distention of the cystic duct, or inflammation associated with the presence of stone. The pain usually occurs in paroxysms with tenderness and pain remaining localized in the right upper quadrant in the abdomen. The history and nature of onset of the acute cholecystic obstruction, in conjunction with a physical examination, should in most instances differentiate this condition from acute pancreatitis. The pain of common duct stone and associated signs and symptoms resemble those of biliary colic, but the presence of jaundice, fever, and chills distinguish this condition from both biliary colic and acute pancreatitis

Acute Coronary Disease

Acute coronary disease and, particularly coronary thrombosis, may resemble important surgical conditions of the abdomen, including gallstone colic, acute pancreatitis, acute appendicitis, perforated peptic ulcer, and acute intestinal obstruction. The presence of dyspnea and the radiation of pain to the sternum or to the arms may be helpful in the differentiation of coronary disease. In acute pancreatitis the pain remains in the midepigastric region and in the left upper quadrant, however, there are cases of acute coronary disease which will have the same symptomatology. Electrocardiograms in the early stages may be the turning point on which the diagnosis will rest. Indeed, the surgeon must be alert to the marked similarity between acute coronary disease and this condition. Realization that coronary heart disease can produce marked abdominal symptoms

like nature is the most important symptom in acute intestinal obstruction Generalized distention of the abdomen usually helps to differentiate between these two conditions In acute pancreatitis there is usually spasm with tenderness in the epigastric and left upper quadrant regions, whereas epigastric muscle spasm and rigidity are not particularly pathognomonic of acute intestinal obstruction The vomiting of fecal material is also suggestive of a high intestinal obstruction. In acute intestinal obstruction the physical examination should reveal the presence of visible peristalsis on the abdominal wall, coincident with the onset of a crampy pain and accompanied by audible sounds Auscultation of the abdomen should also be helpful in making the correct diagnosis of either mechanical or paralytic obstruction In the case of mechanical bowel obstruction the peristaltic note is usually high pitched and is distinguished by evidence of a metallic sound, the presence of peristaltic rushes, and frequently the presence of succussion splashes denoting a dilated loop of bowel On the other hand the paralytic ileus of acute pancreatitis is confined to the upper abdomen and is characterized by epigastric distention and hypo-active peristalsis in that region. The diagnosis of acute intestinal obstruction is aided by roentgenography If the obstruction be mechanical in nature, flat and upright abdominal films should demonstrate the presence of multiple fluid levels in the small bowel which are diagnostic of obstruction in the small intestine. An apparent cause of intestinal obstruction, such as the presence of a hernia, an abdominal scar from a previous operation, or an abdominal mass, may aid in the differential diagnosis.

Acute Appendicitis

In most instances acute appendicitis should not particularly be a problem in the differential diagnosis of acute pancreatitis. In cases of acute appendicitis in which the appendix may be postcecal in position, and also very long so that the body and tip are not too far removed from the gallbladder region, acute inflammatory disease of the appendix may simulate the early stages of acute pancreatitis The pain is confined more to the right upper quadrant and the right side than to the epigastric and left upper quadrant regions. Usually nausea and vomiting are not so severe as in acute pancreatitis Prostration as in acute pancreatitis is not particularly a sign of acute appendicitis

Acute Diffuse Generalized Peritonitis

Acute generalized peritonitis from any cause whatever can be difficult to differentiate from acute pancreatitis Usually, however, the history of an associated illness or abdominal lesion will help to make the correct diagnosis Moreover, the onset of acute pancreatitis is usually more abrupt than that seen in generalized peritonitis The presence of muscle spasm and tenderness over the entire abdominal wall is more suggestive of a generalized process than that usually seen in acute pancreatitis. Diffuse distention associated with a paralytic ileus presents a picture characteristic of generalized peritonitis

Acute Mesenteric Thrombosis

Acute mesenteric thrombosis is probably more common than supposed. This disease usually comes on later in life and is not unlike the picture of acute intes-

Cecil and Levine have stressed most of these points about the clinical manifestations of dissecting aneurysms of the upper abdominal aorta.

TABETIC CRISIS

The gastric crisis of tabes dorsalis may resemble some types of acute pancreatitis. Extreme abdominal pain, nausea and vomiting and mild degree of shock may simulate closely the picture of acute pancreatitis until one examines the patient more thoroughly. A complete examination of the patient will usually differentiate these two conditions. A history of syphilis and the finding of fixed pupils or those which react sluggishly to light, referred to as Argyll-Robertson pupil, are usually present. Moreover, a neurologic examination would demonstrate the flexor plantar reflexes to be absent. The abdominal rigidity usually seen in acute pancreatitis is not present in the gastric crisis of tabes dorsalis. Although the differential diagnosis should be clear, the busy surgeon may fail to make these differential tests, and frequently patients with tabes dorsalis undergo unnecessary surgical exploration.

We have discussed the differential diagnosis of the common medical and surgical conditions which simulate acute pancreatitis. There are other conditions which may produce symptoms not unlike acute pancreatitis. Hemoperitoneum, resulting from a tubal abortion or from a ruptured graafian follicle, may spread rapidly throughout the cavity and cause severe abdominal pain associated with muscle spasm and rigidity. Nausea and vomiting are not characteristic of this condition. In some patients with angina pectoris the symptoms of pain and muscle spasm are referred to the epigastric region. Pulmonary embolus and pulmonary infarction which occur in the lower lobe of the left lung, involving the diaphragmatic pleura, may initiate upper abdominal pain. During the period immediately after onset of these conditions, the correct diagnosis may be extremely difficult. There are other conditions which may, under certain circumstances, be confused with the diagnosis of acute pancreatitis. Some of them are, diaphragmatic hernia with incarceration, the early development of herpes zoster on the left side, acute arthritis of the thoracic spine, traumatic rupture of the aorta, and, rarely, the crisis associated with advancing hemachromatosis.

DIAGNOSIS

From a clinical point of view the diagnosis of acute pancreatitis is most difficult. Almost all authorities agree that prior to the use of clinical laboratory tests on both the urine and the blood, the diagnosis either was not made, was presumptive, or was proved by surgical exploration of the peritoneal cavity. The latter method of diagnosis has not infrequently led to serious consequences and undoubtedly has increased the mortality rate in this condition

During the first 24 hours of an attack of acute pancreatitis a proper diagnosis depends largely on obtaining an elevated value for serum amylase, in conjunction with symptoms of an acute upper abdominal emergency. Other similar diseases, such as perforated peptic ulcer and acute cholecystitis, *must be* excluded even

will direct attention to the thorax and cardiac region Some American clinics have electrocardiography available in the admitting rooms of the hospital, so that this diagnostic measure need not be delayed. Under such conditions it is usually possible to differentiate acute coronary heart disease from acute pancreatitis.

Pneumonia

Pneumonia, particularly, of the diaphragmatic type, may on occasions be differentiated from acute pancreatitis with extreme difficulty. Under such circumstances pneumonia usually has a fairly rapid onset with pain in the chest, cough, cyanosis, dyspnea and usually the development of fever and leukocytosis. Under most circumstances the respiratory and pulse rates are increased and there usually is evidence of labored respiration with movement of the alae nasi In some types of pneumonia, at least in the early stages, râles may not be heard over the lung fields, so that with the referred discomfort to the upper abdomen the differential diagnosis may be difficult. For these reasons a thorough examination of the lung field must be done by the surgeon to eliminate the presence of pneumonia Usually the history and physical findings are sufficient to guard one against making such an error The abdominal symptomatology of pneumonia corresponds to the degree of diaphragmatic pleurisy present. Roentgenograms of the chest will not always help to differentiate these two conditions

Dissecting Aneurysm of the Aorta

Although it is said to be infrequent, dissecting aneurysm of the aorta is being more frequently recognized as a diagnostic problem In the presence of hypertension, dissecting aneurysms of the aorta supposedly develop at the point where the intima of the vessel may rupture. When this occurs, blood usually extravasates between the coats of the large vessel, and a dissecting aneurysm is formed. When this occurrence takes place in the thoracic region, there is usually agonizing pain in the chest, but when it occurs in the first portion of the abdominal aorta, pain may develop to a severe degree in the upper abdomen Characteristically there is excruciating pain in the upper abdomen and a state of shock, similar to the clinical manifestation of acute pancreatitis. Nevertheless, certain observations should help make a clinical diagnosis Usually in a dissecting aneurysm of the abdominal aorta the blood pressure will remain elevated. A helpful sign in the diagnosis of a dissecting aneurysm of the abdominal aorta is arterial obstruction particularly in the branches of the aorta supplying the kidneys and the lower extremities If the aneurysm is progressive in nature, the femoral pulsations in the inguinal regions may be impaired, and the blood pressure in the legs may be reduced to a figure equal to or lower than that in the arms. The absence of electrocardiographic changes is helpful in differentiating this condition from coronary occlusion. The excruciating, boring, abdominal pain characteristic of abdominal aneurysms is usually due to erosion of the bodies of the lumbar vertebrae *If the aneurysm ruptures into the peritoneal cavity with associated* marked abdominal rigidity, shock and death follow. Because syphilis is usually the major cause of aneurysms of the upper abdominal aorta, the physician should carefully examine the patient for signs leading to the clinical diagnosis of syphilis

glycemia is frequently seen and may persist. In the milder forms of pancreatitis hyperglycemia may be transitory. In either event, glucose tolerance tests should be reserved for study after the acute stage of the disease.

In severe cases the blood nonprotein nitrogen may be elevated. The serum bilirubin may also show slight elevation. The white blood count may range from 15,000 to 25,000 with a predominant number of polymorphonuclear cells. Edmondson and Berne have stressed the decreased blood calcium level in acute pancreatitis, occasionally to the point of producing tetany, and this finding may be helpful in determining the degree of fat necrosis.

The blood serum lipase level may be determined. Since 24 hours is required to complete this test it has little practical value in establishing an early diagnosis of pancreatitis.

Urine

Glycosuria, the counterpart of hyperglycemia, is seen in less than 20 per cent of cases with acute pancreatitis When present, it serves as a guide in the management of a temporary or permanent latent diabetic state. In those cases of pancreatitis presenting clinical jaundice, bilirubin and urobilinogen may be found in the urine. Albuminuria is not infrequent Urinary amylase may be increased, but is dependent on kidney function, hence blood amylase is a more reliable test

In any patient with severe upper abdominal pain unexplained by routine methods of history and physical examination, the diagnosis of pancreatitis should always be entertained The essential clinical blood and urine tests are obtained at the same time as routine blood count and urinalysis. The most important single laboratory finding in acute pancreatitis is the elevated blood amylase. The possibility of acute intestinal obstruction or of perforated peptic ulcer may be excluded by roentgenography. Acute vascular accidents, particularly coronary heart disease, may be diagnosed by electrocardiography.

Clinical Features of Chronic Pancreatitis

In general, chronic pancreatitis has not been considered as a distinct pathologic entity, but has usually been regarded in conjunction with chronic cholecystitis, obstructive jaundice due to a stone in the common bile duct, or carcinoma of the ampulla of Vater or of the head of the pancreas. Recently, Comfort, Gambill, and Baggenstoss have emphasized chronic pancreatitis unassociated with disease of the biliary or gastro-intestinal tract as *chronic relapsing pancreatitis.*

Chronic pancreatitis may be defined as a disease entity characterized by recurrent attacks of pain in the upper abdomen, by disturbance of parenchymatous cell function, and by rather specific sequelae, a syndrome which may be limited to the pancreas alone or may be associated with disease of the biliary or gastro-intestinal tract. Attention has been devoted to the pathologic findings of marked interstitial fibrosis and residual cystic necroses of tissue as characteristic of chronic pancreatitis. The term *hydropancreatosis* has been used elsewhere by one of us (V.E.S.) to denote the condition in which the duct

in the presence of an elevated serum amylase before acute pancreatitis can be considered as a sole diagnosis

After the first day of severe illness abdominal fluid may be suspected. If on diagnostic aspiration the fluid is brownish-black ("prune juice") or bloody, this finding points strongly to acute pancreatitis with hemorrhage and necrosis. When tested for amylolytic activity in a manner similar to that used for blood, the peritoneal fluid usually contains amylase. If the physician finds a tender, fixed epigastric mass with radiologic evidence of anterior displacement of the stomach and an elevated left diaphragm in an acute abdominal illness of several days' duration, he can reasonably assume that acute pancreatitis has caused an inflammatory effusion in the lesser peritoneal cavity, and can check that assumption with laboratory tests

At operation the diagnosis of acute pancreatitis can usually be made without difficulty from one or more of the following findings: (1) fat necroses about the pancreas or on the mesenteries and omentum; (2) watery brown exudate or frank blood in the major peritoneal cavity, (3) hemorrhage in or about the pancreas, (4) hard swelling of pancreas, especially in the region of the head of the gland, (5) collection of brownish fluid in the lesser peritoneal cavity, (6) pancreatic pseudocyst.

The various laboratory findings of greatest value in establishing the diagnosis of acute pancreatitis should be discussed in some detail.

Blood

Elevated blood serum amylase and lipase levels are the most significant findings in acute pancreatitis. This increase may be found in the early course of the disease, and may soon return to a normal range, regardless of the pathologic state of the pancreas Rather, after several days illness, the serum amylase level may show no increase in value, a most important point. *An elevated blood serum amylase level indicates pancreatitis, whereas a normal range cannot always rule out this diagnosis.* Although Popper demonstrated that the elevation of the serum amylase and lipase is due to absorption of these pancreatic enzymes into the general circulation via the portal vein and the thoracic duct, the exact mechanism of their liberation from the functional unit of the pancreatic cells is not known The fact that these enzymes are rapidly eliminated from the blood stream would infer that a state of balance between absorption into the blood and elimination from it must exist for a variable period in acute pancreatitis. The enzyme levels may drop precipitously when the pancreas has been seriously damaged with interruption of their production. The serum amylase level is usually higher in the milder forms of pancreatitis and lower in those cases with extensive disease. In the majority of cases the serum amylase test affords an accurate, rapid method of making a correct diagnosis, however, obstruction of the ampullary region of the common bile duct, acute parotitis, and peptic ulcer penetrating into the pancreas are three conditions which may cause the blood amylase level to rise In the presence of pancreatic pseudocysts, the enzyme tests may be normal.

The fasting blood sugar level may be elevated in some cases. When the pancreas is extensively involved, as in hemorrhagic pancreatitis with necrosis, hyper-

represents a sequela of this disease. Many observers (Comfort et al.) believe the calcifications are the result rather than the cause of the disease.

The sequelae which follow chronic pancreatitis are many and variable. There may be temporary disturbance of the acinar cells as shown by the blood amylase and lipase test and of the islet cells as demonstrated by transient diabetes. On the other hand, there may be permanent damage to both of these functional cellular groups which accounts for the marked intestinal disturbances and diabetes mellitus found in long standing chronic pancreatitis. Other sequelae include compression of the duodenum by an enlarged pancreas, compression of the common bile duct giving a picture of obstructive jaundice, and rarely splenomegaly due to pressure on the splenic vein. In some instances there may be direct spread of inflammation from the pancreas to surrounding organs as the stomach, duodenum, liver, and small intestine. Even the peritoneum may be involved as is seen in perigastroduodenitis.

TREATMENT

The practical application of basic physiologic and biochemical principles to the management of pancreatitis has changed the methods of therapy during recent years. The treatment of acute and chronic pancreatitis as well as management of the complications and sequelae will be discussed.

Acute Pancreatitis

Until recently acute pancreatitis was considered a surgical emergency, and either multiple incisions into the pancreas with drainage or drainage of some portion of the extrahepatic biliary tract (cholecystostomy or choledochostomy) were performed. On rare occasions surgeons have advocated drainage of both the pancreas and extrahepatic biliary tract. Many observers believed that surgical treatment of acute pancreatitis was unjustified and gradually a more conservative approach has evolved. This change of attitude was not abrupt, and there are still a few who advise surgical intervention. In general, surgical drainage of the pancreas or of the bile ducts during the acute stage of the disease has carried a mortality rate of about 50 per cent, whereas conservative attitude in the management of pancreatitis has reduced the mortality.

Since the serum amylase test usually confirms the correct diagnosis, failure to diagnose emergencies requiring surgery is less apt to occur, and therefore conservative therapy is not a dangerous program. Currently, conservative measures are advocated until complications which require surgical intervention, such as pancreatic pseudocyst, intra-abdominal abscess, or collections of pancreatic fluid arise. Associated regional gastro-intestinal or biliary tract lesions can be treated after the patient has recovered from the acute pancreatic episode.

Nonoperative or Conservative Therapy. Because no clinical method is available to differentiate acute edematous pancreatitis from acute hemorrhagic pancreatitis, the clinician must practice conservative measures on each patient entering the hospital. A period of close observation should indicate the general behavior of the disease, and usually within four to six days the clinical course becomes fairly well established.

system is dilated above a point of obstruction with extensive atrophy of the parenchyma.

Incidence and Exciting Factors. Chronic pancreatitis may begin in childhood or late in life, but usually starts most frequently in the third or fourth decade. It occurs more often among males than among females, the ratio being about 6.1 (Comfort, Gambill, and Baggenstoss). Dietary indiscretions and alcohol appear to initiate the acute attacks. Size, weight, and obesity are probably not precipitating factors. Bustos (1945) stressed the possibility of focal and systemic infection as a likely cause of chronic pancreatitis, however, Comfort et al. (1946) minimized infection as an etiologic hypothesis.

Symptoms and Physical Findings. Although there are no pathognomonic symptoms and signs of chronic pancreatitis the collective findings of pancreatic pain, dyspepsia, steatorrhea, diabetes, and occasionally a mass palpated in the epigastric region should direct attention toward this organ.

The pain in chronic pancreatitis usually starts abruptly, but is not always severe It has been described as constant and burning, and usually, though not always, is provoked by food and alcohol, in contrast to the pain of chronic peptic ulcer, which usually is alleviated momentarily by the ingestion of food. The seizures of pain in chronic pancreatitis may continue over various periods of time, from a few days to as long as 10 to 20 years. The pain, usually steady, is frequently located in the epigastrium, although it is not uncommon in either of the upper abdominal quadrants. As in acute pancreatitis, pain in chronic pancreatitis may radiate transversely across the epigastric region, through to the back, or occasionally to the left costal angle.

The physical findings vary with the stage of the attack, which in many instances is so mild that there are no significant signs Fever and leukocytosis, and in some cases even shock, are found Usually there is some degree of muscle spasm in the upper abdomen In a very thin patient with long-standing chronic pancreatitis an enlarged or acystic pancreas may be palpated as an indefinite mass. Jaundice occurs in almost half of the cases with chronic pancreatitis

Laboratory Features Transient or persistent glycosuria represents a form of diabetes mellitus. Albuminuria is not uncommon

Blood studies frequently show an anemia, and blood volume may fall below a normal level. Leukocytosis is a variable and an unimportant diagnostic feature. The presence of an elevated blood sugar and a diabetic type of glucose tolerance curve is extremely helpful from both a diagnostic and therapeutic point of view. The serum bilirubin determination may reveal subclinical or clinical jaundice The blood serum amylase test may or may not be elevated, and this test is not nearly so valuable as in acute pancreatitis Hypocalcemia noted in acute pancreatitis is not present in chronic pancreatitis.

Examination of the stool is important, and the clinical picture of steatorrhea should warrant thorough investigation. Stools may vary from large, bulky, whitish, fatty ones to those of normal consistency Microscopically, undigested starches (amylorrhea), proteins (azotorrhea) and fats (steatorrhea) may be found.

Roentgenologic studies of the gallbladder, stomach, duodenum, small intestine, and colon may demonstrate associated pathologic conditions. A roentgenogram of the pancreas will in about 50 per cent of cases reveal calcification which

therapy remains a problem. These cases always suggest the likelihood of necrotic pancreatitis. Of the two therapeutic attitudes, one group believes that the pancreas, if necrotic, tends to perforate into the lesser peritoneal cavity; hence, this anatomic location should be drained early through the foramen of Winslow or by a retroperitoneal approach. The second group argues that operative interference cannot be tolerated by such patients and that surgical exploration only increases the mortality rate.

Some observers state that cholecystectomy may reduce biliary pressure. Other groups argue that cholecystectomy should be done primarily, after which choledochotomy associated with prolonged drainage of the common bile duct (choledochostomy) is indicated (Mayo; Archibald; Judd).

According to recent opinion, operations upon the neighboring gastro-intestinal and extrahepatic biliary tracts in the presence of acute pancreatitis are inadvisable. Those holding this opinion prefer to wait for the pancreatic process to subside and, assured of this, to evaluate the status of the gallbladder, liver, stomach, and duodenum for the presence of such conditions as cholecystitis, cholelithiasis, choledocholithiasis, and penetrating peptic ulcer, which should then be corrected by surgical methods.

From this discussion it is apparent that definite rules regarding therapy cannot and should not be made. A logical approach to this problem may be found in the integration of the history, physical and laboratory findings, response to therapy, and clinical course of the individual patient. Careful observation of the patient will determine the best therapeutic course.

Chemotherapy. As yet no analytical figures are available which indicate the effect of modern chemotherapy upon pancreatitis. For the prevention of suppurative disease of this organ we believe chemotherapy should be used in the treatment of acute pancreatitis.

Penicillin may be given at the rate of 300,000 units daily. The method and site of administration may be decided by the individual clinician Streptomycin given intramuscularly at the rate of 0 5 gm twice daily may be administered. Sulfa derivatives may be given intravenously in doses of 2 5 to 5 gm., but should not be given by mouth Although in a majority of cases with acute pancreatitis bacterial cultures of the diseased tissue cannot be obtained, the condition is so serious that administration of chemotherapeutic agents remains practical and is justified.

Sphincterotomy Cholangiograms obtained at operation (choledochotomy) may be used advantageously to demonstrate common duct obstruction, spasm of the sphincter of Oddi, and the common channel into the pancreatic duct system When cholangiograms demonstrate spasm or obstruction of the sphincter of Oddi associated with a reflux of radiopaque material into the pancreatic duct, section of the sphincter has been advised (Colp, Doubilet, Mulholland). More work should be done in this field before we can draw final conclusions.

Chronic Pancreatitis

The treatment of chronic (relapsing) pancreatitis may involve conservative or surgical measures.

Conservative Treatment. This therapy is purely palliative, and consists of controlling pain, gastritis, and dyspepsia, and correcting pancreatic insufficiency.

Conservative treatment is specifically concerned with two problems: (1) to institute measures which will diminish excessive pancreatic secretion, and (2) to allay spasm of the sphincter of Oddi.

1. Since food in the stomach stimulates pancreatic secretion, the patient at bed rest should receive nothing by mouth. In order to prevent gastric juice (chiefly hydrochloric acid) from affecting pancreatic secretion, continuous gastric aspiration should be instituted early and maintained as long as indicated, changing the Levine tube periodically. Since both hyperglycemia and hypoglycemia may affect pancreatic secretory function, control of the blood sugar level by the combined use of intravenous glucose and administration of insulin is important. Pain is best controlled by the use of demerol which has an atropine-like action and therefore does not stimulate the vagus nerve. Atropine paralyzes the cholinergic nerve fibers which excite pancreatic secretion. Ephedrine also will diminish pancreatic secretion (Cole). Morphine should be avoided when possible because it usually fails to control pain and stimulates pancreatic secretion (Elman and Popper).

2. Antispasmodics such as atropine and nitroglycerine may aid in reducing spasm of the sphincter of Oddi. Novocainization of the paravertebral sympathetic ganglia may diminish pancreatic function and may also inhibit the spastic contractions of the sphincter of Oddi. Several authorities have advocated this procedure early in the course of the disease (Popper and Gage).

Water and electrolyte balance can be maintained by the parenteral administration of physiologic salt solution, blood plasma, and whole blood if indicated. Lindeman (1940) referred to the fact that an antitryptic factor was present in the albumin fraction of blood. One might assume that large quantities of blood plasma, or more specifically the albumin fraction, may prove beneficial in those patients who develop hemorrhagic (necrotic) pancreatitis. Routine administration of solutions of glucose is contraindicated since hyperglycemia may stimulate pancreatic secretion. Calcium salts may be given intravenously to control tetany. Chemotherapy should be given in all cases of acute pancreatitis on a prophylactic basis.

Operative Treatment. Although most observers (Elman, Mell, Cole, Morton, Popper, and others) agree on conservative treatment in the milder forms of acute pancreatitis (edematous variety), there is no universal agreement about the exact management of acute necrotic pancreatitis. In general, the consensus of opinion indicates that operative procedures are less favored now than in former years. Surgery is indicated when a localized collection of fluid becomes manifest, when an intra-abdominal abscess is apparent, when a pancreatic pseudocyst becomes palpable, or when an abscess develops in the lesser peritoneal cavity. If indicated, operation should assure sufficient and adequate drainage of the complication, but exploration should not be extensive. An abscess of the lesser peritoneal cavity is more difficult to diagnose and more difficult to drain adequately than one in the greater peritoneal cavity. Operative procedures should not replace the good therapeutic measures of conservative management. Gastric aspiration, transfusions of whole blood or plasma, and chemotherapy should be continued postoperatively.

Whether those patients with acute pancreatitis who are admitted to the hospital in circulatory collapse should or should not be submitted to surgical

have lowered the over-all mortality of acute pancreatitis, but the figures remain discouragingly high. Paxton and Payne (1948) reported a mortality of 33 per cent in 307 patients. The current mortality in acute edematous pancreatitis, diagnosed mainly on clinical grounds, probably averages about 15 per cent, while the mortality in hemorrhagic and necrotic pancreatitis remains above 60 per cent.

In an attempt to evaluate the effect of operative treatment on mortality figures, Morton (1940, 1945) has compiled the results following early and late operation in acute pancreatitis. In 911 cases submitting to early operation, the mortality was 49 per cent. In a smaller group of 161 cases submitted to delayed operation there was a mortality rate of 18 per cent. In 41 cases of edematous pancreatitis treated by operation, the mortality was 27 per cent, while of 29 such cases treated without operation, not one patient died.

These figures indicate the seriousness of acute hemorrhagic pancreatitis as well as the high mortality rate when operations are performed early. Within the near future the results of conservative therapy will be better evaluated, as will the role of chemotherapy in lowering the death rate from this disease.

PROGNOSIS

The prognosis of acute pancreatitis can be considered grave Any patient surviving the initial attack cannot be assured that future episodes will not occur. Recurrent attacks are observed in 7 to 30 per cent of cases of acute pancreatitis In pancreatic abscess or cyst formation a persistent pancreatico-cutaneous fistula may occur. The islands of Langerhans may be so extensively damaged that diabetes occurs in about 11 per cent of the cases. Some patients suffer pancreatic asthenia (Whipple, 1924) and die within a few weeks of the onset of acute pancreatitis. Liver disease, particularly fatty degeneration, may be a sequel to this syndrome.

Acute pancreatitis may be the precursor of chronic relapsing pancreatitis, of which the prognosis is poor. Chronic disability and invalidism from the severe persistent pain of this disease are the chief concern. Rehabilitation of these patients offers a challenge to the medical profession.

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Pain in chronic pancreatitis is best relieved by demerol, because it does not stimulate the vagus nerve and has fewer addicting properties. Nitroglycerin and ephedrine may relieve distress, but are not always successful. During acute exacerbations treatment consists of the same therapeutic measures outlined under the treatment of acute pancreatitis. Since alcohol and rich, fatty foods may initiate attacks these two factors should be controlled. Alcohol should be completely restricted and the diet should consist of bland foods low in fat content.

Several sequelae of chronic pancreatitis may warrant medical attention. Diarrhea may be adequately controlled by low fat diet containing 50 gm. or less of fat each day. Pancreatin, 2 to 10 gm. three times daily (enteric-coated tablets) may control diarrhea. Hypoproteinemia and malnutrition can be corrected by high protein diet, high caloric intake, and administration of pancreatin. Diabetes should be treated by diet and insulin. Marked hemorrhage from the gastro-intestinal tract may require blood transfusions; nutritional anemia may be controlled by diet regulation and iron therapy.

Surgical Treatment. There are several indications for surgical intervention in chronic pancreatitis. Chronic duodenal obstruction must be corrected by duodenojejunostomy or gastroenterostomy. Occasionally, partial pancreatectomy may be required to correct the obstruction. Chronic obstruction of the common bile duct requires correction by either choledochoduodenostomy, cholecystogastrostomy, or by choledochojejunostomy with the Roux-Y method. Pancreatic abscess, single or multiple, requires external drainage. Pancreatic cysts should be drained, either by marsupialization to the exterior or by internal drainage into the stomach, duodenum, or jejunum. Gastric hemorrhage may require subtotal gastrectomy. Pancreatic abscess arising from a penetrating peptic ulcer may require subtotal gastric resection combined with partial pancreatectomy. Single pancreatic calculus obstructing the duct of Wirsung near the duodenum is rare but can be corrected by pancreatolithotomy. Multiple pancreatic calculi are common and, if they produce chronic disability with severe pain and dyspepsia, partial and even total pancreatectomy may be required (Clagett, Nuzum, Whipple, Zinninger, Child, Leopard, and Orr). If the symptom of pain is not relieved by these procedures either thoracolumbar sympathectomy or vagotomy or both may be indicated.

MORTALITY

Prior to the widespread use of the serum amylase test when many cases of acute edematous pancreatitis were not recognized, the over-all mortality in acute pancreatitis was considered to be more than 50 per cent. The mortality in edematous pancreatitis, diagnosed at operation or necropsy, was about 30 per cent, whereas hemorrhagic and necrotic pancreatitis was 60 to 70 per cent fatal. Before the introduction of antiobiotic drugs 50 per cent of cases with suppurative pancreatitis died. Mortality figures should differentiate among the pathologic types of the disease to be completely significant. Recent clinical reports have included under the category of acute edematous pancreatitis many cases which are presumptively diagnosed on the basis of an elevated serum or urinary amlyase in conjunction with a consistent clinical picture and which are not subjected to operation or necropsy. These broader diagnostic criteria

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Carcinoma of the Endometrium

Carcinoma of the Endometrium

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INTRODUCTION

Definition

Because of the anatomic divisions of the uterine cavity, it has become common practice to call carcinoma arising in the endometrial cavity by such descriptive terms as carcinoma of the body or of the fundus of the uterus They are used synonomously with carcinoma of the endometrium. The mucous membrane lining the uterine cavity is composed of simple columnar epithelium which contains many glands. Carcinoma arising from this histologic background is almost invariably an adenocarcinoma. Because cancer arising within the confines of the uterine cavity is restricted in its spread by the normally thick muscle walls of the uterus a more hopeful prognosis may be offered than for carcinoma arising in the cervical portion Carcinoma of the endometrium has neither the lethal growth potentialities nor the rapid progression of cancer of the cervix.

INCIDENCE

Though carcinoma of the fundus occurs far less frequently than cancer of the cervix, it makes its appearance sufficiently often to be regarded with more respect than it is frequently accorded. The Bureau of Census statistics for 1942 records 16,393 deaths from cancer of the uterus. Of these, cancer of the endometrium is responsible for 20 per cent or over 3,000 deaths in one year.

The disease is primarily one of the postclimacteric period but may occur during the reproductive era. Randall found, for example, that, excluding menorrhagia from such pathologic entities as fibroids, erosion of the cervix, or polyp, 9 1 per cent of women bleeding from a normal sized uterus will have carcinoma of the endometrium on curettage. When these factors are included the incidence drops to 2.3 per cent. After the menopause 4 out of every 10 women who consult their physician because of the reappearance of bleeding after one or more years of amenorrhea will have endometrial carcinoma. Not all bleeding after the menopause is secondary to carcinoma of the endometrium, but enough of it is, and its import is serious enough to regard bleeding in the postmenopausal age group as due to carcinoma of the endometrium until proved otherwise. It would be well to remember that cancer of the cervix may also occur in this age group. The frequency of carcinoma of the cervix in relation to the incidence of cancer of the endometrium varies in reports from the literature Mahle placed the ratio at 1 2 4, Masson 1:3, Taylor 1:3.4, Smith 1:4 5, Meigs 1 5, Novak 1:8, Pack 1:8 2, Scheffey 1:10.8. A ratio of 1:5 will be somewhere near the average ratio. It is obvious then that, though

AGE INCIDENCE

While carcinoma of the endometrium occurs for the most part in the post-climacteric period it may appear as early as the "teens." Taussig, commenting on Novak's and Yui's reported cases, gives unmistakable evidence in 2 cases that the early manifestations of carcinoma may closely follow the menarche. In both instances excessive bleeding required curettage at 13 and 15 years. Hyperplasia that could bear watching was noted in one. The other responded to progestin therapy. Within two years excessive bleeding again recurred and was relieved by curettage for another two-year period. The diagnosis of carcinoma was finally made in both instances six years after the initial episode of excessive bleeding.

The majority of cases reported in the literature will show an occasional case below the age of 30, with perhaps 5 to 8 per cent of the total appearing between 30 and 40. Norris and Dunne record the age incidence in 286 cases as follows:

	Per cent
20 to 29 years	1.5
30 to 39 years	6.7
40 to 49 years	18 3
50 to 59 years	46.3
60 to 69 years	21.3
70 to 79 years	5 9

Approximately 20 to 25 per cent of the total cases of cancer of the endometrium appear during the reproductive period or below the age of 50. Smith found 84 per cent of 307 consecutive cases after the age of 50, while 44 per cent were over 60 Masson places the figure at 75 per cent, while Scheffey declares for 79 per cent The average age is probably close to the figure of 56 years noted by Scheffey.

The menopause is characteristically delayed in patients with cancer of the endometrium. Moss found moreover that patients who developed intra-uterine cancer had a more prolonged menstrual life than the women without it. Not only was the menopause delayed but the menarche appeared on an average of two years earlier. It is thus possible to postulate on the one hand that perhaps there is a basic difference in the type of uterus that will develop carcinoma, and, on the other, that the delayed menopause permits this sort of an organ to be stimulated by whatever the carcinogenic agent may be for a longer period of time.

ETIOLOGY

CHRONIC IRRITATION

In the past chronic irritation was the popular etiologic theory in the development of cancer within the uterine cavity. Carcinoma of the endometrium not infrequently is found in the atrophic uterus in association with a pyometrium Chronic endometritis could, therefore, always be observed where cancer of the endometrium was present. It is probable that this theory was based on a

the peak age incidence for carcinoma of the cervix is lower than that for carcinoma of the endometrium, the difference in the frequency of its appearance is such that it too must be ruled out as a cause of bleeding in the postclimacteric period. It would be well to have our minds focused on the possibility of uterine cancer as an explanation of bleeding at this time. Inasmuch as 25 per cent of women with cancer of the endometrium have the disease before the menopause, any bleeding in a woman beyond the age of 40 should be considered as due possibly to cancer of the uterus.

Economic Status

In this regard it is interesting also to make a comparison with cancer of the cervix While cervical neoplasm is most frequently encountered in the clinic, carcinoma of the fundus is commonly found in women seen in private practice. There are many speculations as to why this may be so The patient with cancer of the cervix, being in the poorer economic status, may receive poorer obstetrical care both at the time of delivery and in the postpartum period These women are inclined to marry early and have repeated pregnancies There is a possibility that deficiencies in both diet and hygiene may play an etiologic role in increasing the incidence of carcinoma of the cervix Certainly the patients with carcinoma of the fundus are exposed to better nutrition and hygiene.

Race

Again in contrasting carcinoma of the cervix to that of the endometrium, different racial tendencies are apparent. Negro women, subject to many of the vicissitudes of patients in the lowered income groups, may have carcinoma of the cervix in as high an incidence as 10 per cent. Fibroids are commonly observed among them in a higher percentage than one encounters for the rest of the population Fibroids are likewise thought to be secondary to overstimulation by estrin The same factors are advanced as an etiologic explanation for carcinoma of the endometrium, yet the incidence of cancer of the fundus among Negroes is about 3 per cent

The converse is true in the Jewish population· carcinoma of the cervix is almost unknown among Jewish women The incidence of carcinoma of the endometrium, however, is higher among Jewish women than gentiles Scheffey found that 5 5 per cent of 127 cases of cancer of the endometrium were among Jewish women. There is thus some unknown factor in the Jewish constitution or manner of life which protects the woman from cancer of the cervix while increasing the likelihood of their developing cancer of the endometrium.

Marital Status

The percentage of nulliparous women among patients with cancer of the cervix is about 10 per cent in contrast to the 28 to 35 per cent found for those with neoplasm of the endometrium This contrast may have something to do with the fact that carcinoma of the endometrium has a tendency to develop in the unused or nonphysiologic uterus. Unfortunately repeated pregnancies, which may contribute to the etiology of cancer of the cervix, do not appear to protect a woman from developing cancer of the endometrium.

in the transition of hyperplasia to carcinoma only if a proper substrate exists. These patients have abnormal bleeding at the time of the climacteric about three times as frequently as the expected incidence. Many of them have had previous curettage for the correction of irregular bleeding tendencies preceding the menopause. Taylor says this incidence is as high as 19 per cent. The number of instances of carcinoma developing in the nulliparous uterus provides additional confirmatory evidence that we are dealing with a substrate which, if sufficiently stimulated over a long enough period of time, might develop a tendency to malignant transformation. The delayed menopause noted in this group of women with a peak incidence coming between 50 to 55 years against a normal of 48 years suggests that there is an endocrine factor at work. It could be that the uterus is exposed over a longer period of time to estrogen stimulation

Functioning Ovarian Tumors. The repeated association in the literature of hyperplasia, carcinoma of the endometrium, and functioning tumors of the ovary such as granulosal cell and theca-cell carcinoma, and also pseudomucinous cystadenoma infers that there is a definite relation between estrogen stimulation, the development of hyperplasia, and the development of carcinoma of the fundus. These tumors not only secrete estrogen but actually contain estrogen in measurable quantities as shown by the chemical analysis of Banner and Dockerty on eight theca-cell tumors in comparison with a like number of normal ovaries. The amount is appreciable, but smaller quantities may have a maximal effect on the endometrium or breast for the action is unopposed by progesterone. Thus there appears to be some evidence for the carcinogenic influence of the secretion from these tumors.

Other evidence of measurable quantities of estrogen recovered in the 24 hour urine specimens of women with carcinoma of the fundus is offered by Herrell In 80 per cent of the urine specimens from these patients better than 5 rat units were recovered. Jones and Brewer feel that this is to be expected from normal males or castrate females and cite Frank et al. as well as Dingamanse et al. to prove their contention.

Experimental Evidence. Experimental evidence in animals concerning the carcinogenic effect of estrogen has not been confirmatory as a general rule. Cystic hyperplasia but not carcinoma appears in the rat, mouse, guinea pig, rabbit, and monkey after administration of estrogen in large amounts over long periods of time. Recently, however, Greene and Saxton have produced tumors in the endometrium of old rabbits, which apparently arose in the mucosa and spread by local extension and metastases and were associated with estrogen-like effects in the adrenal, thyroid, breast, and ovary Inasmuch as these could be attained only when old rabbits with a previous history of eclampsia were employed, the resultant liver damage may have had something to do with their inability to inactivate estrogen, thereby resulting in prolonged unopposed stimulation

"Unopposed" Estrogen. Whenever estrogen stimulation is mentioned, the qualifying term "unopposed" is added, on the basis that corpora lutea are not found in the ovary. Jones and Brewer find in the ovary of the patients in the premenopausal age active corpora lutea, with secretory changes in the endometrium conforming to the proper date for the cycle. This ability of the remaining

misinterpretation of the pathologic differences between the endometrial response secondary to infection and the normal endometrial reaction to hormonal stimuli. Willis, in discussing the possible role of chronic infection as a provocative agent in the development of endometrial carcinoma, could find no evidence that *such violent chronic infections as postabortal or postpuerperal sepsis predisposed* to carcinoma of the fundus Meigs states that true chronic inflammatory changes are actually rare in the body of the uterus The chronic irritation theory has given way completely to the highly speculative theory as to the role played by an overproduction of the ovarian hormone estrogen in relation to the development of both hyperplasia and carcinoma.

THE ESTROGEN THEORY

It is by no means established that estrogen whether unopposed or not is the cause of hyperplasia, on the one hand, or that hyperplasia is a necessary precursor to the development of malignancy of the fundus, on the other.

There appears to be considerable clinical evidence that estrogen does play a major etiologic role The frequent association of such associated pathology as fibroids and polyps with endometrial carcinoma is noted. Ovarian tumors such as the granulosal cell and thecal cell types are thought to secrete estrogen and are found in increasing frequency with carcinoma of the endometrium. There is much suggestive evidence to be gathered from the clinical history to indicate the relationship Clinical observations based on the results of hormone therapy are interesting, on the other hand, animal experimentation is lacking and the actual source of the estrogen in the postmenopausal age group is in doubt.

In view of the relative frequency of stimulation of the uterus by estrogen either naturally or synthetically through the use of hormone therapy and the relative rarity of carcinoma of the endometrium, it is obvious that the evidence for hyperestrinism as the etiologic explanation is inconclusive unless we assume the presence of a proper substrate sensitized to the activity of estrogen. The following pages will consider in detail, some of the evidence for the estrogen theory

Associated Pathology The frequent association with fibroids and the occasional finding of carcinoma with uterine polyps suggest again that malignancy may have arisen on the basis of a pre-existing hyperplasia of the endometrium in a uterus subject to continuous overstimulation by estrogenic activity. The biologically similar nature of hyperplasia and carcinoma with its tendency to invade has been noted by Taylor While no significant etiologic relationship has been attached to adenomyosis as an etiologic agent, nevertheless fibroids, proliferative endometrium, and adenomyosis coexist in a higher percentage in patients with carcinoma of the fundus than in the normal woman Kaufmann, et al. have reported carcinoma arising in adenomyoma Willis attributes the findings to the unphysiologic state of the uterus.

Clinical Evidence. Corscaden and Gusberg further observe that there is a measurable difference in the physical appearance and menstrual history of the women who develop carcinoma, giving added evidence to the observation of Herrell that the unopposed action of estrogen on the endometrium may result

hormone and thus activate the ovary to produce this cortical hyperplasia. would appear from these proposals that even the source of estrogen stimulat is subject to speculation.

Jones and Brewer doubt that estrogen stimulation, unopposed or otherw actually has anything to do with the development of endometrial carcino It seems unreasonable to them that estrogen stimulation sufficient to prod cancer should not activate the remaining portions of the endometrium to a gre extent than they believe that it does. Novak, on the other hand, reports t this stimulation of the endometrium actually does produce focal areas wit it which stimulate carcinoma. Telinde is not in complete agreement. Thus do is thrown upon the entire theory for the role played by estrogen itsel questioned.

Hormone Therapy. In addition to the endogenous estrogen so much estro is being used as replacement therapy that it is well to consider this sou Most investigators believe that the amount ingested is not sufficient in quan to be carcinogenic. In view of the experimental evidence indicating that i perhaps the continuity rather than the size of the dosage that is the impor factor in the development of carcinoma, it is now common clinical practic interrupt the therapy for one week out of the month. But it may neverthe be possible to take small dosages over too long a period. Haagensen has rece seen 7 cases of carcinoma in the male breast following estrogen therapy carcinoma of the prostrate. Inasmuch as carcinoma of the male breast is a r tively uncommon occurrence, these observations are significant.

In view of the conflicting observations from competent students of problem, it is obvious that while the estrogen theory has more to recommen than the chronic irritation theory, definite proof is lacking that estroge the carcinogenic agent in the development of intra-uterine cancer.

THE ROLE OF HYPERPLASIA

The same inconclusive evidence is present when one considers hyperp as an essential precursor of endometrial carcinoma. Not all pathologists ar agreement as to what hyperplasia really is Some will admit that the endomet of carcinoma of the fundus is stimulated, but will deny that it is true hyperpl The clinical evidence is again the strongest link in the chain of evidence. two conditions are known to coexist and occur naturally in the presence of f tioning ovarian tumors. Again the clinical history is of utmost importance the assumption of the existence of proper substrate is essential if the theo estrogen in relation to hyperplasia is to appear logical There appears to be doubt that the relationship is a definite one, though all the evidence is not per cent confirmatory or complete. The following pages will present the evid for and against hyperplasia, including its bearing on such pathology as fib and uterine polyps which are so closely associated with hyperplasia and end trial carcinoma.

General Considerations. One reason for the considerable difference of opi as to the role played by hyperplasia in the development of carcinoma of endometrium may be attributed to the failure to consider hyperplasia i pendently of the factors which may produce it. Considerable variation in

portion of the endometrium, uninvolved in carcinoma, to respond in the normal manner to the follicular hormone and to progesterone, they regard as evidence against hyperestrinism as a cause for carcinoma. Novak believes that hyperplasia in the reproductive period has no relation to carcinoma, but perfectly typical actively growing hyperplasia is found in women far beyond the menopause. This he believes is due to excessive estrogen stimulation and may be precancerous if a predisposition to the development of malignancy exists

Estrogenic Sources The source of estrogen is in doubt in his mind for he regards the ovaries as senile and raises the suggestion of an extragenital source of estrin such as the anterior pituitary. It is true that previous castration by surgery or radiation does not prevent the development of carcinoma in the retained uterus. Elton et al. record authentic cases It is interesting that all have the stigmata of the unphysiologic uterus. Randall feels that these cases should not be offered as evidence that adenocarcinoma can develop in a uterus that has not been previously stimulated by estrogen, unless the vaginal mucous membrane indicates by atrophy that estrogen stimulation has been absent for a long period of time Castration in the young has been known to be followed in months or years by resumption of the menstrual flow apparently due to extragenital production of estrogen. These facts would tend to confirm Novak's supposition

Smith and Hertig have recently advanced a new theory for the continued production of estrogen originating in the ovary of the postmenopausal period.

Hertig, considering the aging ovary in women past 50, finds rare evidence of follicular activity, primordial or otherwise Yet there is a group of women who have ovaries of women 10 years their junior with much evidence of hyperplasia of the stroma of the cortex of the ovary, even to the finding of granulomas in the cortex, representing perhaps an abortive attempt on the part of the ovarian stroma to continue some follicular-like activity in the absence of primordial ova. Smith has noted this stromal activity as early as 45 years, but its greatest incidence, 87 per cent of 180 postmenopausal women, occurred after the age of 50. *Where the most marked activity was observed, endometrial activity or* outright malignancy was found In fact, stromal hyperplasia in the ovary proved a most frequent finding in association with carcinoma in a ratio of better than 2.1 for the controls

While complete proof is lacking, endometrial proliferation may rightly be interpreted as indicating secretion of estrogen by the ovary, inasmuch as the extragenital sources, such as the adrenal cortex, do not excrete enough to produce proliferation When the follicles in the ovary are exhausted, the ovarian stroma remains as the only source of whatever estrogen is secreted, according to Smith's and Hertig's observations

Novak and Yui postulated a theory that carcinoma itself might act as an estrogen factor and be responsible for the frequent finding of hyperplasia occurring long after the menopause, but inasmuch as this hyperplasia is also found where no cancer exists, *they fall back* on an extragenital source for estrogen stimulation. Smith and Hertig ponder the same question, and speculate as to whether the products of protein catabolism incident to the breakdown of the existing carcinoma may not set off the anterior pituitary to liberate the luteinizing

carcinoma. In this group, however, the endometrium is so stimulated that even the most experienced pathologist is concerned about the malignant possibilities. Where hormones have been administered the problems of the pathologist are magnified But whether the pathologic findings are those of hyperplasia or not, the suggestion of malignancy is so strong that practical considerations call for hysterectomy.



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Postmenopausal Period. In the postmenopausal period many borderline cases exist, and suspicion becomes centered on hyperplasia as a precancerous lesion. Hyperplasia before the menopause, Novak believes, is of little or no significance. After the menopause the hyperplasia, or the endocrine dysfunction responsible for it, most strongly predisposes to the development of carcinoma, in his opinion Whereas the incidence of hyperplasia in normal women beyond the menopause, taking 55 years as an arbitrary age, is about 5 per cent, hyperplasia in women with carcinoma appears in 21 per cent or perhaps higher.

Typical actively growing hyperplasia may be found far along in the menopause. With the peak incidence between 50 and 55 years in women developing carcinoma of the fundus, it is obvious that these uteri have been under estrogen stimulation for a longer period of time. Moreover this *priming* with estrogen is more likely to be unopposed. All grades of estrogen effect may then be seen in the senile endometrium as observed by Novak. The thin atrophic endometrium with the fibrotic stroma and moderately dilated glands gives way to thick glandular epithelium with an active stroma under the influence of this

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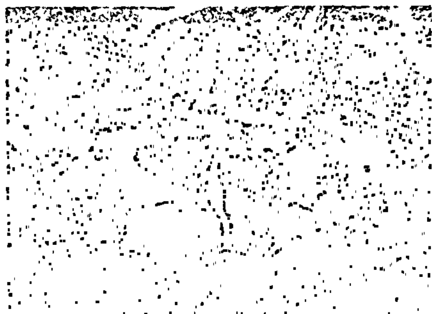


FIG 1 —Atypical hyperplasia with cystic gland formation Metaplasia with mucin production in glands regarded as benign

not respond in the same degree to a common stimulus. By and large, the less pronounced phases are readily identified and fortunately predominate in the bulk of patients with hyperplasia Most authors are in agreement with Novak that there is nothing in the ordinary Swiss-cheese endometrium to resemble carcinoma, nor does there appear to be any tendency for it to become carcinomatous This is particularly true during the reproductive period

The Reproductive Period. The great difficulty here seems to be that the evaluation of hyperplasia as a precursor becomes clouded by the tendency to consider the histology independent of the cause Jones and Brewer find ample evidence, confirmed by Taylor, Randall, and Herrell, that the uninvolved portions of the endometrium participate in a normal manner to the stimulation of the hormones They, therefore, will not subscribe to the theory that the unopposed action of the estrogen leads to hyperplasia and thence to carcinoma. That the endometrium is stimulated is unquestioned, but that it represents other than physiologic hypertrophy is doubted.

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secrete estrogen in sufficient quantities to induce postmenopausal bleeding secondary to endometrial hyperplasia. This is particularly true of women past the age of 60, in whom periodic bleeding is not uncommon and thick polypoid endometrium a frequent finding. The association with carcinoma is more than one would expect from mere chance. Many writers have commented on this coexistence of the two tumors, including Kirschbaum, Traut and Butterworth, Porter and Bramball. Mussey et al., found the association to be about 10 times



Fig. 4 —Cut section of granulosal cell carcinoma of right ovary with associated adenocarcinoma of endometrium.
(Courtesy of Dr. Arthur Hertig.)

as high as one would expect if the two tumors were coincidental findings. The incidence proved to be about 27 per cent in the menopause age where the tumors are commonly found.

Clinical Evidence. While the relationship between hyperplasia and carcinoma of the endometrium is questionable, there is ample circumstantial evidence from the clinical side for judicious speculation. From a consideration of the clinical histories, there appears to be a definite type of individual who may develop carcinoma of the fundus. In all probability the menopause has been marked by prolonged periods of markedly increased flow which has persisted beyond the customary 48 years of the climacteric. Crossen finds that this delay in the time of the menopause increases the likelihood of the development of fundal malignancy in the ratio of 4:1 for the normals. Corscaden and Gusberg note that 39 per cent of postmenopausal women who developed carcinoma suffered a bleeding abnormality during the climacteric, or about three times the normal expectancy. At the time of curettage, 31 per cent had a hyperplastic endometrium.

unopposed estrogen activity. It is in this group, therefore, that borderline cases are found and errors of interpretation are made. The differences obviously depend on what is interpreted as hyperplasia.

Coexistence of Carcinoma and Hyperplasia. It is in this group also that carcinoma and hyperplastic endometrium may be found to coexist in the same uterus, with evidence at times of the gradual transition from one to the other. Such older writers as Schroeder, Shaw, and Cullen deny this coexistence. They

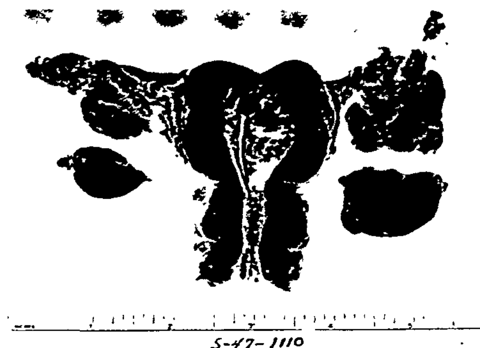


Fig. 3.—Sections of bilateral carcinoma of endometrium.

would agree with Burch that they had never seen hyperplasia and carcinoma present at the same time, nor hyperplasia as a precursor of neoplasm. Payne, however, places the incidence of coexistence of the two pathologic entities at 10 per cent. Where the remaining portions of the endometrium were available for study after hysterectomy for carcinoma, Novak found all gradations of hyperplasia up to and including carcinoma in 40 per cent. There is such coexistence. Ewing, Taylor, Meyer, Randall, Schroeder, Adler, Fluhman, and Stephenson all have commented on the association, but whether it occurs as frequently as reported by Novak is debatable. Some authors have suggested that the relationship is no more than pure coincidence. This wide discrepancy may be explained by the failure to establish the minimum criteria for a diagnosis of hyperplasia.

Functioning Ovarian Tumors. Perhaps the circumstantial evidence most difficult to overcome for those who doubt the significance of hyperplasia in relation to uterine cancer is the increasing incidence noted in the literature of the association of functioning ovarian tumors with endometrial carcinoma. There can be little doubt that both the granulosal-cell tumor of the ovary and the thecoma

secrete estrogen in sufficient quantities to induce postmenopausal bleeding secondary to endometrial hyperplasia. This is particularly true of women past the age of 60, in whom periodic bleeding is not uncommon and thick polypoid endometrium a frequent finding. The association with carcinoma is more than one would expect from mere chance. Many writers have commented on this coexistence of the two tumors, including Kirschbaum, Traut and Butterworth, Porter and Bramball. Mussey et al., found the association to be about 10 times



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It is a well known clinical observation that carcinoma of the endometrium does not develop while a woman is having hot flashes, particularly if the vaginal mucous membrane indicates by its atrophic lining that estrogen deprivation exists. The converse of this statement is also true. Where evidence of estrogen activity persists into the menopause and is accompanied by functional bleeding, the patient should be regarded with suspicion, for her chances of having carcinoma are better in the ratio of 3:5 than her contemporary with an atrophic vaginal wall

Many patients who subsequently develop carcinoma of the endometrium have a history of irregular bleeding during the reproductive period. One or more diagnostic curettages performed for other than miscarriage is not an uncommon history. Taylor places the incidence at 19 per cent The number tends to parallel the clinical severity of the symptoms and the degree of proliferative activity of the endometrium Where the symptoms and the histologic findings are mild, cure frequently results from a single curettage Where more marked hyperplasia is encountered, repeated curettages are the rule.

The history of repeated curettage in the past can only be considered as circumstantial evidence in attempting to work out a causal relationship between hyperplasia and carcinoma It is a well known fact that cancer of the uterus may be very slow in growing. It is thus possible that the original pathology may have been missed at the time of the curettage, either by the surgeon or the pathologist. If the curettage took place within a year of the final diagnosis, the basic pathology was overlooked probably more from inadequate curettage than a faulty interpretation of the sections

Endocrine Imbalance. While the history of previous abnormal bleeding of sufficient severity to call for curettage or even radiation to control it may not be advanced as other than suggestive proof that hyperplasia and carcinoma are related, it does suggest an endocrine imbalance. The average fertility is generally reduced as compared with carcinoma of the cervix, and the percentage of nulliparous patients is nearly doubled Fibroids are associated with carcinoma in 28 per cent of those patients with carcinoma of the endometrium It is not that the fibroids themselves, or perhaps the etiologic agent responsible for them, are important, but rather that fibroids are another bit of evidence which suggests that the substrate in these patients causes them to be abnormally sensitive to the varied stimuli which may institute malignant change

Corscaden and Gusberg believe that the type of woman who will develop carcinoma has something in her genes that makes her cancer-susceptible. It may be that estrogen is the carcinogenic factor, but whether opposed or not it becomes effective only when it has the proper substrate to act upon. Certainly some such qualifying interpretation is necessary to explain many incongruities which otherwise would be an acceptable etiologic theory There are many instances of hyperplasia but carcinoma develops in relatively few. These women, despite the fact that they develop hyperplasia to the point where they are frequently indistinguishable from microscopic cancer, rarely develop malignancy of the uterus Corscaden reports five such instances where carcinoma developed years after prolonged estrogen administration Nearly all gynecologists interested in malignant disease can produce one or more cases of this sort. But when one

considers the myriads of women in this age group who are regularly exposed to the stimulating effect of this known carcinogen, it is indeed surprising that more cases of carcinoma do not make themselves evident. Thus to make the estrogen-hyperplasia-carcinoma theory tenable we must presuppose that a genetic substrate is present which makes these patients susceptible to the development of malignancy.



Fig 5 —Curettings showing hyperplasia and estrin effect four years after the menopause.

Fibroids

Concerning the relation of uterine fibroids to uterine carcinoma, there can be no doubt that the two coexist but the etiologic relationship may be questioned The doubt arises in connection with the role played by estrogen in the development of malignancy within the uterus.

Association with Carcinoma. If the problem is approached from the point of view of the carcinoma, the association will vary from 20 to 40 per cent with the majority of authors reporting an incidence of about 35 per cent.

Healey	40 per cent
Taylor-Miller	40 per cent
Scheffey	38 per cent
Stacey	37 per cent
Masson and Gregg	36 per cent
Falls	35 per cent
Norris and Dunne	34 per cent
Bowers	28 per cent
Graves	25 per cent
Barnes	24 per cent
Miller	20 per cent

On the other hand the commonly accepted frequency of carcinoma found in a large series of fibroid uteri is about 2 to 4 per cent. Adair reports 2 per cent, Barnes 4 per cent, and Morris and Max 5 6 per cent.

The association then is a common one but in all probability there is little relationship to carcinoma. It may be that the presence of fibroids is an indication of the growth potential for that uterus. If this is true there is little reason for removing fibroids over 5 cm as advocated by Healey. Willis confirms a well



Fig. 6—Same case as Fig 5, two years later Adenocarcinoma grade II, persistent estrin administration.

known observation that fibroids occur in over 20 per cent of women past the age of 30 The coexistence of fibroids and carcinoma appears to be coincidental. The relationship is no more evident when the size of the fibroid is considered, according to Masson. Where leiomyoma is so commonly found it would be surprising that carcinoma and fibroid did not coexist. Carcinoma may invade a uterine fibroid and in this manner give rise to the misconception that carcinoma arose in the fibroid, but it is difficult to see histologically how anything but a sarcoma could appear. The incidence of adenomyosis with fibroids and hyperplasia is higher than one encounters in women without adenocarcinoma. No etiologic relationship is attached to the finding. The relationship is probably due to the propensity of the susceptible uterus to develop malignant as well as benign tumors.

Submucous Fibroid. Cancer is not infrequently seen developing in the mucous membrane overlying a submucous fibroid. Ewing has reported a number of such incidences. The inference is that the mucous membrane is stimulated by the trauma of the underlying fibroid It is possible that the ulcerative and inflammatory changes present in the submucous fibroid might give rise to a stimulus sufficient to predispose cancer on the basis of the chronic irritation theory. However, it is difficult to see how a subserous intramural fibroid could produce

such irritation and certainly not all fibroids in association with carcinoma are submucous.

Clinical Evidence. There is a clinical observation, however, that arouses some speculation concerning fibroids as an etiologic factor. While the coexistence of cancer of the endometrium and fibroids is not uncommon, the relationship is rare in the cervix. Noble, quoted by Novak, reported in 1906 that leiomyoma appeared eight times more frequently with cancer of the endometrium than with neoplasm of the cervix in 2,274 unselected fibroids. This report suggests that some form of stimulation is at work which is more selective for the uterine endometrium

Estrogenic Source. The source of this stimulation may be hormonal and is, in all probability, estrogenic. The relationship is an indirect one through the association with hyperplasia. Fibroids are more readily produced in animal experiments by continued unopposed estrogen stimulation than is hyperplasia or carcinoma. Mussey and Dockerty observed that prolonged estrogen stimulation in the absence of progestin will produce not only fibroids but polypoid proliferative endometrium. This fact can be established clinically among women receiving estrogen therapy for disorders of the menopause. These two factors are likewise observed in association with granulosal carcinomas. Fifty per cent of the women with granulosa-cell carcinoma of the ovary have fibroids, or about twice the number found in the control series. It is, therefore, inferred that the estrogen secretion of the ovarian tumor is responsible for the common finding of hyperplasia and the relative frequency of carcinoma of the endometrium, at least among granulosal and theca-cell tumors.

Doubt of Relationship. Not all authors are in agreement that fibroids are the result of estrogen stimulation nor that the origin of carcinoma of the fundus and fibroids can be traced to this source. Jones and Brewer found but one instance of hyperplasia in 100 fibroids examined. Herrell admits that estrogen stimulation will produce a proliferative endometrium that may provide the basis for the development of carcinoma, but does not believe the endometrial response can be called hyperplasia. With estrogen withdrawn at the time of the menopause the fibroid is supposed to reduce in size. This is advanced as an argument for hyperestrinism as a cause of fibroids. Meyer suggests that while this may be true it is also possible that the shrinkage may come about through a reduction in blood supply. Bowers does not believe that estrogen is the sole element in the creation of fibroids. A disordered ovarian function secondary to inflammatory processes within the uterus or adnexa may result in an overproduction of estrogen by the ovary and the relation to fibroids may be brought about in this manner. Hyperplasia was found in only 11 per cent of 476 fibroids.

Clinical Observations. Regardless of the etiologic relationship, it is well to remember that fibroids and carcinoma do coexist. Abnormal bleeding at the time of the menopause should be considered as due to the carcinoma and not the fibroid, lest valuable time be lost in instituting proper treatment. Norris and Dunne found among premenopausal patients with a fibroid and carcinoma of the endometrium that the average duration of symptoms was six months longer when fibroids were present.

It is axiomatic that every hysterectomy for fibroids be preceded by a diagnostic

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Fig 7.—Carcinoma of one horn of bicornate uterus.



Fig 8—Diagrammatic drawing of carcinoma of one horn of bicornate uterus.

curettage and every specimen be opened at the operating table to avoid an inadequate operation. Graves believes it important to explore the uterine cavity where the use of x-ray or radium is contemplated for a fibroid complicated by carcinoma, or sarcomatous degeneration may be further activated by the influence of radiation. The important point to remember is that the presence of a fibroid may mask the existence of carcinoma of the endometrium

POLYPS

Incidence Based on the experience of polyp formation in other parts of the body, particularly the intestine where 40 per cent showed malignant change, *polyps within the uterine cavity have come to be regarded as potentially malignant.* Actually malignant change within a uterine polyp is a rare finding. Norris and Vogt could trace the change from benign to malignant in but 3 of 104 uterine polyps examined. Brindley found 13 instances where coexistence appeared, but Hirson notes that in many instances malignancy was found with none observed within the polyp itself. It is this coexistence, coupled with the history of repeated removal of polyps in a uterus that subsequently develops carcinoma, which has given support to the contention that carcinoma of the endometrium may arise from a pre-existing polyp. Iseki believes that it may arise from a polyp and collected 17 such cases. Three of these were believed to be primary with 2 doubtful, while 9 showed secondary malignant degeneration of what had been considered primarily as simple polyps.

Histologic Pattern. The histologic diagnosis is not an easy one. There is such marked proliferation of closely packed and irregularly branching glands with the stroma compressed into narrow strips that the similarity with adenocarcinoma is striking

These changes noted within the endometrium would in all probability give rise to the diagnosis of malignancy, but where they are localized to a polyp, the significance is not great As Hirson notes, the loss of gland individuality is probably the most important single diagnostic finding, for the difference in the cell structure may be difficult to recognize Iseki bases his diagnosis of malignancy within the polyp on the finding of areas of adenomatous growth which begin to break through the protective capsule surrounding a group of glands. Occasionally it may start on the surface but rarely is it primary all over its surface. The significance if this atypical metaplasia of the surface epithelium is in doubt. Hirson regards this as a precancerous state, while Geist believes that inasmuch as all polyps are pedunculated, they are hence subjected to trauma and resulting infection. The metaplasia then is in response to the infection and only simulates carcinoma

Mode of Spread. In general, the malignant change should begin at the base and either extend upward into the polyp or downward to invade the underlying musculature. It is therefore, important to examine the base of the polyp removed at curettage Rarely carcinoma may be found in a cancer-free uterus with the malignancy confined to one portion of the polyp.

Polyps found within the uterus do not have the same malignant potential as those found elsewhere within the body, for seldom does carcinoma of the endometrium arise from a pre-existing polyp.

his patients with fundal carcinoma were obese, and Smith found 28 per cent weighing more than 160 pounds. Corscaden points out that not only are these women obese but they look larger than they actually are, for they are prone to have small hands and feet and large rounded hips. This is not by accident but rather an indication of a basic endocrine imbalance. Robinson, commenting on the relation of body types to other diseases such as cardiovascular disorders or thyroid disease, states that body build is a deep seated change indicative of disorder in the neuro-endocrine system and the biochemical reactions of the body. The incidence of growth and time of appearance in mouse tumors has a definite relation to carbohydrate intake as noted by Tannenbaum. While the relationship between carcinoma of the endometrium and obesity is not direct, the association seems to be relatively constant. Life insurance statistics, for example, indicate that people who are overweight when past middle age are more likely to die of carcinoma than the average. Moss observes, however, that perhaps the factors tending to control the weight may be more important than the actual weight itself.

Diabetes. Inasmuch as obesity and diabetes are frequently associated, it is not surprising to find that 11 per cent of Scheffey's series of patients with carcinoma of the endometrium had diabetes. There is nothing about cancer itself that predisposes to diabetes, according to Marble. It does have a relation to obesity. John found that 66 per cent of 172 obese females had abnormal glucose tolerance curves. The patients with carcinoma of the endometrium tend to have diabetes not because they have cancer but because they are overweight.

Hypertension. Like obesity, hypertension is commonly noted in determining the relative operability of patients with cancer of the endometrium Moss notes a definite increase in the diastolic and systolic pressure among broad-chested people. As the body expands laterally, as it does among patients with carcinoma of the fundus, the incidence of hypertension increases. The finding of hypertension among this group is a natural sequela, not an accidental association

It is thus evident that postmenopausal bleeding appearing in a fat patient who has hypertension and diabetes should be regarded as significant because of its common association with carcinoma of the endometrium.

The Late Menopause. There is much circumstantial evidence to indicate that the delayed menopause so commonly associated with carcinoma of the fundus is of diagnostic significance. The average age of patients developing cancer of the endometrium is six and one-half years older than those with cancer of the cervix. Crossen and Hobbs find the late menopause has a definite association with carcinoma.

Age at Menopause	*Fundal Cancer*	*Normal*
	56 cases	2,291 cases
36 to 40 years	2 per cent	12 per cent
40 to 45 years	4 per cent	26 per cent
45 to 50 years	30 per cent	41 per cent
50 to 55 years	60 per cent	15 per cent

It has been suggested that the delayed menopause may provide a longer period of time during which estrogen may stimulate a susceptible uterus with

Coexistence with Carcinoma The coexistence of carcinoma and uterine polyp is of importance in establishing a diagnosis. Fahlund and Broders found in a study of 236 cases of postmenopausal uteri that the incidence of endometrial polyps was about 8 times greater in cases with carcinoma than in those without disease. It is easy then to explain the symptoms of abnormal uterine bleeding on the recovery of a polyp at the time of curettage. The presence of a polyp may mask the unrecognized coexistence of carcinoma within the uterus.

Clinical Observation The following case may serve to emphasize the dangers in attributing the cause of the abnormal bleeding to a polyp alone. An unmarried woman of 52 observed vaginal bleeding, intermittent in character, over a period of three months. A small polyp could be seen presenting from the uterine canal at the cervix. Curettage failed to produce adequate material to explain the history of bleeding which, while intermittent, was of appreciable quantity. A total hysterectomy with removal of both adnexa revealed a bicornate uterus with a rudimentary cervix entering a sleeve compartment at the apex of the vagina. The normal cervix and communicating uterine cavity were negative, but the contralateral horn of the bicornate uterus was completely filled with carcinoma.

SYMPTOMS

Inasmuch as little information will be forthcoming from a general physical examination, it is important to establish some sort of a working background from which it may be possible to recognize the type of individual who may be expected to develop malignant disease Much helpful information can be obtained from the history of these individuals.

For example, Randall has called attention to the fact that women with carcinoma who experience excessive bleeding at the time of the delayed menopause rarely show the signs of atrophy of the vaginal mucous membrane that one might expect in a woman in the menopause This type of patient should be kept under scrupulous observation

Likewise Corscaden and Moss have independently made observations on the body type common to the patients who subsequently develop carcinoma of the uterine body Serious concurrent disease is frequently noted among these patients Bowing and Fricke found that 75 per cent of the women presented to them for radiation therapy were refused surgery largely because of obesity, hypertension, cardiovascular disease, or diabetes rather than because of the extent of the disease This coexistence appears to be more than accidental. Before considering the symptomatology it seems pertinent to discuss the background to the development of carcinoma of the endometrium.

Predisposing Factors

Body Types. Obesity It is a common observation where operability is under consideration that the patients with carcinoma of the endometrium tend to be obese. Moss, using standard tables for age and height, found the women in his series to be about 10 per cent overweight on the average. This, according to Corscaden, is about 9 times the probable error. Frank noted that 35 per cent of

The Irregular Menstrual Pattern. In a further suggestion that endometrial carcinoma may appear in the unused or unphysiologic uterus, it is interesting to observe the number of patients who exhibit a past or present abnormal bleeding pattern. Such bleeding abnormalities are common for example among nulliparous patients. There is recorded history of previous treatment for fibroids or menorrhagia secondary to endometrial hyperplasia. One-third to one-half of patients who developed carcinoma of the endometrium before the menopause



FIG. 9—Carcinoma of fundus arising 15 years after radium for bleeding in presence of a benign fibroid.

show long-standing gross abnormalities of menstruation. The same history is obtained among those who develop carcinoma of the fundus in the postmenopausal period Excessive and irregular bleeding histories are more common than one encounters in the normal population. When such a history exists, the likelihood of the patient developing carcinoma within the uterus is about 3 times the normal expectancy.

Previous Radiation. Many of these patients have received radium for alleviation of the profuse irregular bleeding some years previously. Corscaden checked the histories of 1,100 women who had the menopause induced by radium given for benign bleeding. After six and one-half years, 15 had developed carcinoma of the uterus The number with cancer of the endometrium was three times the expectancy. One might argue that the subsequent carcinoma arose as the result of previous radiation. Luker reported 14 such instances from the literature. Late development of carcinoma elsewhere in the body has been observed arising in areas which had been the site of intensive radiation years before. It is not infrequently observed, for example, on the skin following external radiation It is conceivable that a similar situation might arise within the uterus. Randall records

the resultant increase in carcinoma. Randall could find but 8 per cent of women without cancer in the uterus who continued to bleed after the age of 50. On the other hand 35 per cent of the patients who developed carcinoma had bleeding after the age of 51. In this group it is interesting to observe that the patient experiences nothing in the way of hot flashes, and upon inspection reveals a bluish moist vaginal mucosa indicative of continued estrogen activity. Because of these observations, linked with the not uncommon finding of leiomyomas, errors in diagnosis are often made, for the bleeding may be attributed to the fibroid, which in turn may conceal the presence of carcinoma. Likewise the patient regards the irregular bleeding occurring after the menopause as a resumption or continuation of the normal catamenia and avoids medical consultation.

Because of the failure to consider carcinoma of the endometrium as the most important cause of abnormal bleeding at the time of the climacteric Smith found that 9 per cent of the total number of 360 patients with carcinoma had been mismanaged. Ergot had been given in one instance for a history of six months' bleeding occurring 14 years after the menopause. There were several instances of abdominal exploration and oophorectomy for postmenopausal bleeding where no preliminary curettage had been performed. In some instances a curettage had been done without a definite cause being found to explain the bleeding, yet recurrence of the bleeding was ignored because of the negative findings at the initial curettement. Such a patient should be labeled as highly suspicious and followed up religiously. Another common source of error was noted in the number who had roentgenologic treatment without a preliminary curettage. Naturally the patient does not want to undergo even a diagnostic curettage. Such an outline of treatment is, therefore, very popular but highly dangerous Menorrhagia at this time may be functional or secondary to a benign lesion but it may be the only malignant symptom

Marital Status. According to the statistics of the British Clinical Cancer Research Committee, women who are married are less likely to develop carcinoma of the endometrium than those who are unmarried. Inasmuch as the United States Census reports from the New York-New Jersey area state that 12 per cent of women over the age of 35 are unmarried, it is evident that women who develop carcinoma of the endometrium marry about as frequently as the normal population, though in some series the percentage of single women runs as high as 25 per cent The number of infertile marriages, however, is definitely higher than the expected incidence placed at 17 per cent by the same census reports. From multiple reports in the literature it appears that 25 to 40 per cent of women who develop carcinoma of the endometrium will be nulliparous

Whereas a definite relationship exists between pregnancy and cancer of the cervix, no such correlation is noted for the endometrium Corscaden found 38 per cent nulliparas among patients with endometrial carcinoma as against 16 per cent for cancer of the cervix This figure is about eight and one half times greater than the probable error.

Parity then certainly cannot be regarded as an etiologic factor in the development of carcinoma of the endometrium except as it suggests a faulty substrate. It is probably this element that is important rather than sterility itself.

Economic Status. It is a well known clinical observation that carcinoma of the endometrium, in contrast to carcinoma of the cervix, is more frequently encountered in private practice. Corscaden found this to be true in the relation of about 2 to 1. No further significance can be read into this observation.

Summary. It is evident that certain observations may be extracted from the histories of patients with carcinoma of the endometrium which may prove helpful in establishing a diagnosis. Inasmuch as little aid may be acquired from a general physical examination, reliance must be placed in large part on the history. If, for example, we keep in mind that bleeding abnormalities at the climacteric are three times as common among patients who have carcinoma of the fundus as in normal women and that such patients are four times as likely to develop such a cancer, then one's attention becomes focused on this group.

We have noted from the history that many obese women of sound economic status are either unmarried or infertile. Frequently these women have a long history of abnormal menstrual bleeding preceding a delayed menopause marked by excessive flow. Such a patient is a likely candidate for carcinoma of the endometrium.

Bleeding

The most important single symptom of cancer of the endometrium is abnormal uterine bleeding. The character of the bleeding depends upon the age of the patient at the time the malignancy develops. About 75 per cent of the patients with fundal carcinoma will be in the postmenopausal period with 25 per cent still in the reproductive era. Bleeding in some form is present in practically 100 per cent and appears as the first symptom in approximately 80 per cent.

The character of the bleeding varies. It may manifest itself as: (1) Irregular bleeding with a tendency to increasing quantity of flow; this type of bleeding is characteristic of that group of women which develops carcinoma before the menopause. (2) Irregular spotting, usually of no great quantity. It is frequently observed after straining on defecation or micturition. Occasionally there is a history of a fall Rarely is it aggravated by coitus or douches. (3) Minimal spotting or staining in the postmenopausal period. This is commonly intermittent in frequency (4) Sudden gushing of blood not uncommon as an intermenstrual phenomenon among the younger group but occurring also years after cessation of bleeding.

These types of bleeding are well known to the medical profession yet the [illegible] seems at times [illegible] the lay public [illegible]enopause, but [illegible] appears to be more than a fair amount of lethargy on the part of the medical profession and a tendency to explain away the symptoms rather than to investigate them. While cancer of the endometrium may appear to be slowly growing, early diagnosis and treatment reflect in the survival rates just as positively as they do for malignancy anywhere else.

Premenopausal Irregular bleeding is the rule in the reproductive period, marked by a steadily progressive increase in the amount of flow. There are so many factors that enter to bring about confusion in diagnosis, such as the presence

in the literature 4 such patients who developed uterine carcinoma one year after intra-uterine radiation in amounts of 1000 to 1800 mg. hours. The time element is important, for some of the recorded instances of carcinoma following radiation are so recent that the relationship must be regarded as questionable in that it is not completely assumed that the carcinoma was not overlooked at the time of the curettage.

Nevertheless carcinoma of the endometrium has followed the application of



Fig 10—Carcinoma of fundus arising 14 years after radiation for benign uterine bleeding Note stenosis of the cervical canal

intra-uterine radiation Scheffey collected from the literature 65 cases of fundal malignancy with a previous history of radiation. Many surgeons advise radiation for patients with a history of irregular and profuse bleeding if at the time of curettage no gross abnormalities are found in the endometrium Whether there is a direct etiologic relationship is questionable. An indirect approach may be considered in that there are some surgeons who believe that disordered ovarian function may produce a greater degree of estrogen stimulation than the normal ovary. Such observations have been made on patients who have received roentgen treatment as well as those treated with radium alone. It is possible, but unlikely, that intra-uterine radium might so tip the balance in the ovary that hyperplasia and carcinoma might develop at a later date.

In all probability previous radiation does not actually give rise to carcinoma of the endometrium, but at the same time it may be said that it is of no value in the prevention of cancer that may later develop within the uterus.

It would appear that the basic relationship lies in the fact that the underlying substrate is at fault The abnormal bleeding for which the radiation was given is an indication that the uterus is abnormally sensitive to stimulation and if such stimulation is continued over a long period of time the uterus contains within itself the potentiality of developing malignant disease.

Hormone Therapy. Perhaps the most troublesome causes of postmenopausal bleeding other than carcinoma is that secondary to the use of estrogenic hormone. It is widely used for hot flashes or simply to make women feel better. In more instances than not the therapy is prescribed by a friend rather than a physician. Bleeding occurs as a result of prolonged administration or from withdrawal of the hormone. The physician falls into the trap of explaining the appearance of bleeding after the menopause by the use of the drug, without considering the possibility that continued estrogen may either result in or actually cause cancer of the endometrium. We know it may conceal it. There is some evidence that it may cause it. This is based largely on the observation that the granulosa-cell carcinoma known to secrete estrogen is commonly found in association with fundal malignancy.

Certainly too much estrogen therapy is being prescribed for disorders of the menopause, including bleeding, without first ruling out the possibility of an already existing carcinoma. In far too many instances the drug is prescribed without the benefit of a pelvic examination, much less a curettage.

Not all women who take estrogen therapy will develop carcinoma of the endometrium. If they did, malignancy would be a much more common occurrence.

Clinical Observations. There is enough evidence, both in animal experimentation and among humans, suggesting that prolonged estrogen stimulation upon a sensitive soil may reap a malignant harvest, to advise caution in the widespread use of the hormone over any extended period. If there is any suggestion of cancer susceptibility noted in the family history, the hormone should not be given at all. Where it is employed in this age group, pre-existing carcinoma should be ruled out and the estrogen given on a planned schedule calling for interruption in the continuity of administration At the present time common practice calls for estrogen administration daily for three weeks followed by one week when no hormone is given. If bleeding follows withdrawal of the drug a curettage is immediately indicated, for the hormone may be concealing the presence of carcinoma.

While it is true that estrogen therapy may induce profuse bleeding at the menopause, either through prolonged administration or withdrawal, the danger comes in the possible misinterpretation of the cause of such bleeding. Inasmuch as estrogen may either produce carcinoma or hide its presence, *it is axiomatic* that postmenopausal bleeding should be regarded as due to carcinoma of the endometrium until proved otherwise.

Discharge

Type. The next most common symptom of carcinoma of the endometrium is a vaginal discharge which may precede the onset of bleeding. Its diagnostic significance cannot be stressed too much, for there are many other entities that may explain the findings. The discharge is often clear at first. The watery type of discharge may appear in bursts as the patient strains at heavy exertion or following micturition or defecation At times the discharge may be preceded by indefinite cramps as though the uterus were attempting to expel its contents through a stenosed cervical canal. Later the discharge becomes seropurulent and may increase in amount. If a pyometra exists, as it commonly does with uterine

of fibroids and the frequency of endocrine imbalance, that some delay in seeking medical advice may be anticipated. Some of the delay must be attributed to the medical profession who place a faulty interpretation on the cause of bleeding. Norris and Dunne noted in 1936 an average duration of symptoms in this group of 22 months. With the advent of the cancer educational program instituted by the American Cancer Society, this has been appreciably reduced though the same elements accounting for the delay are present. Miller reporting in 1941 found that the average waste of time among the group with abnormal bleeding was about seven months before seeking medical advice with another four month delay on the part of the physician, so that the average duration of symptoms antedating treatment was about 11 months.

Postmenopausal In the postmenopausal epoch vaginal spotting is by far the most common symptom This may be continuous or intermittent. It is frequently noted following defecation or micturition Because it is small in amount and infrequent in appearance, the patient is reluctant to consult her physician or she becomes lulled into a sense of security by the inconstancy of the symptom But where this symptom arises as a primary symptom one year after the menopause it is of extreme importance, inasmuch as two-thirds of these patients will prove to have malignancy, according to Ward.

Scheffey could find only 3 instances among his patients with postmenopausal carcinoma who did not demonstrate this irregular spotting. In one the first symptom was a metastatic nodule in the vagina, while another had pain as the first symptom because of an extensive hematometra.

The average duration of symptoms in this group has been only slightly improved by the cancer educational campaign, for it is still fairly evident that the significance of postmenopausal bleeding is not sufficiently appreciated. Whereas Norris and Dunne noted an average duration of symptoms of 16 months, Scheffey, reporting in 1943, found the delay to be about 13 months The improvement is not dramatic.

Occasionally the patient may experience a sudden severe hemorrhage from the uterine canal years after the cessation of the periods. Not infrequently this may be due to other pathology than carcinoma, but where this history is obtained it is more likely due to carcinoma than any other cause.

Other Causes There are of course other explanations of postmenopausal bleeding than carcinoma, but it is still the primary one and obviously the most important In a changing medical world the old medical school axiom still holds — that postmenopausal bleeding is due to carcinoma of the endometrium until proved otherwise Too often the bleeding is explained on the basis of the presence of a polyp or senile vaginitis Hypertension is known to produce uterine bleeding at this age In recent years the recurrence of periodic bleeding is commonly attributed to the functioning ovarian tumors such as the theca-cell and granulosa-cell carcinoma In the premenopausal period Randall believes that less than one in 10 diagnostic curettages will unearth a carcinoma of the endometrium. But where this procedure is carried out after the menopause and no other explanation of the bleeding is forthcoming, 60 per cent will have carcinoma. It must never be forgotten that even in the postmenopausal age group the possibility of carcinoma of the cervix is of utmost importance both statistically and practically.

Anemia

Though the primary symptom is that of bleeding, neither this factor nor the necrosis of the tumor is sufficient to show in the blood picture to any great extent. About one-third of the patients will have less than 12 gm. of hemoglobin. Anemia may be found in extreme necrosis of tumor and death from hemorrhage is not unknown. As a rule, anemia is not a common finding.

Urinary Symptoms

Where the disease in its late stages invades the parametrium one would expect an increasing incidence of compression of the ureter with resultant hydronephrosis, pyonephrosis, and uremia. But even in the late stages of the disease this series of events is a rare finding and in direct contrast to carcinoma of the cervix. The actual incidence of such complications is about 13 per cent, with the percentage variation having some relation to the rate of growth and pathologic grade of the tumor. It is almost unknown with the low grade adenocarcinomas, while a limited percentage of anaplastic tumors may produce urinary symptoms.

PHYSICAL EXAMINATION

Obesity

Attention has already been called to the type of build commonly encountered among patients who are susceptible to the development of carcinoma of the endometrium. Patients who are obviously overweight for their age and height tend to have, according to Moss, a heavy lateral build. Corscaden elaborated the findings, noting that these women not only are fat but appear heavier than the scale indicates because of their small hands and feet and rounded hips. The average increase in poundage is about 18 pounds or 10 per cent of their body weight. Perhaps because of this heavy lateral type of build, obesity and hypertension go hand in hand.

Double Primary

Inasmuch as intra-uterine cancer is not frequently associated with primary carcinoma elsewhere, it is of utmost importance that the general physical examination be complete. Taylor and Becker found double primary malignant tumors in 4 per cent of their whole series, confirming Warren and Gates' reports based on 1,078 necropsies One-half of the other carcinomas associated with intrauterine malignancy arose in the breast in Taylor's series, whereas Smith found 50 per cent appearing in the ovary Metastatic nodules present in the vaginal mucosa, often occurring near the urethral meatus, may represent malignant extensions from the large bowel. The double association is not uncommon but it is well to remember that primary carcinoma of the large bowel may metastasize to the vaginal outlet without carcinoma being within the uterine cavity. The pathologic report of adenocarcinoma is confusing unless it is accompanied by the pathologist's note that a primary lesion should be sought in the intestinal tract. Two recent cases have been encountered illustrative of this finding. In

carcinoma, it may be more or less noticeable depending on the degree of stenosis. A gradual progression to a brownish or blood-tinged type of discharge is commonly noted, though frequently this is the first symptom. The secretion only becomes malodorous as the tumor within the uterus breaks down and becomes necrotic

Clinical Correlation Murphy has attempted to correlate the symptom of discharge to the pathologic grade of the tumor and finds that the incidence of this symptom tends to vary with the structural grade of the tumor. Anaplastic carcinomas, for example, are least likely to show discharge, while discharge commonly accompanies malignant adenoma and adenocarcinoma. That it is a late manifestation may be deduced by the observation that 47 per cent of the inoperable patients noted a vaginal discharge as against 30 per cent of the operable The accuracy of the statistical data is attenuated by such associated findings as endocervicitis and senile vaginitis. Most authors agree that little statistical significance can be attached to such findings

Pain

Type and Severity. This symptom is rather difficult to evaluate. It occurs in about one-third of the cases, according to Healey and Brown. Obviously some of the symptom of pain is secondary to other pelvic lesions. It is commonly regarded as a late symptom, but Meigs found that over 60 per cent had a low abdominal dull ache associated at times with a bearing-down sensation and pain in the low back. The pain is of varying degrees of severity. Occasional cramplike pains may appear in the early stages of the disease as the uterus attempts to expel some of its contents Pyometra and hematometra are not uncommon findings. The sense of pressure and lower abdominal discomfort are heightened by their presence, and complete relief may follow an acute cramplike pain which results in expulsion of the uterine contents.

Clinical Correlation It has been common practice to consider that pain in association with carcinoma is in direct relation to the extent of the disease and that *severe pain is an indication that we are dealing with a hopeless and* inoperable case It is assumed that pain occurs as the growth invades the parametrium and involves the sacral plexus. Murphy found a definite percentage increase as the disease became histologically more malignant. Likewise the incidence in inoperable cases was about double that of the operable group.

Nevertheless among 56 cases who had pelvic pain, only 16 had extra-uterine involvement, while 43 with extension of disease beyond the uterus had no pain at all. It would, therefore, seem unwise to be guided in the choice of treatment by the symptom of pain. As regards prognosis, pain should be considered as a factor only as it is evaluated in relation to other factors bearing on prognosis.

Weight Loss

Inasmuch as carcinoma of the endometrium appears to be relatively slow in its development, the general appearance of the patient does not reflect the extent of the disease. Weight loss, noted in about 11 per cent, is not a significant factor. *Jeffcoate found that while the average weight loss was about 17 pounds, nearly* a third had lost as little as four pounds.

conversely, that women with excessive bleeding during a delayed menopause should be regarded with suspicion if the vaginal mucosa shows evidence of activity.

Examination of Uterus

Examination of the uterus concerns itself with size and mobility as well as possible parametrial extension of the intra-uterine carcinoma. The base of the broad ligament should be palpated in relation to the uterocervical segment both by vagina and rectum. Pliability of the pelvic floor is of particular interest, together with the presence or absence of nodular thickening. The mobility of the uterus is in direct relation to parametrial fixation or to the size of the uterus. In an uncomplicated carcinoma of the uterine body, the size of the uterus is in most instances normal Unfortunately, the common association with pyometra or fibroids so changes the size of the uterus that it is difficult to establish any clinical classification that is effective, as can be done for the cervix. There are many such classifications based on the size of the uterus that appear to be reasonably effective in evaluating the prognosis. There can be no doubt that in the field of surgery for malignancy, the size of the initial lesion is the most important single prognostic factor outweighing duration of the disease and grade of the disease It is possible, within limits, to measure the extent of the disease within the cervix by employing such a clinical classification. But where the carcinoma of the endometrium remains hidden within a blind cavity such as the uterine canal, where it can be neither seen nor felt, we have no conception of the site of the malignancy, much less of its size. Any classification must then be based on the size of the organ containing the carcinoma, not on the size of the malignant lesion itself Certainly an enlarged fibroid uterus with a small carcinoma should not give a worse prognosis than a small uterus with a uterine cavity completely filled with cancer. It is much like basing a classification on the size of the breast rather than on the lesion within the breast.

Clinical Classification

Some degree of accuracy in prognosis, however, appears to follow a clinical classification based on the size of the uterus. Healey believes it is useful in determining the prognosis in cases treated by radiation. If the type of treatment is dependent upon the stage of the lesion, then classification through consideration of the size of the uterus is the only way it can be done. It is of no help to consider prognosis in the light of the size of the lesion after the uterus has been removed Fricke and Bowing have developed four stages to be employed as a clinical classification:

1 The uterus is not enlarged and is movable.
2. The uterus is enlarged but still movable. There is no infiltration.
3. Entertains 3 possibilities:
   (a) the uterus is not enlarged but there is limited mobility and infiltration of both parametrium;
   (b) the uterus is enlarged and fixed, owing to the infiltration of one parametrium to the pelvic wall;

contrast to the above, one of Scheffey's patients presented a nodule at the vaginal introitus as the first indication of a carcinoma of the endometrium. This type of metastasis has an important bearing on treatment, for it suggests retrograde lymphatic spread.

Associated Pathology

Much of the associated pathology may be recognized upon physical examination. Evidence for fibroids, ovarian tumors, carcinoma of the cervix, vulva, and breast, polyps, pyometrium, procidentia, and anemia all may be elicited by a general physical examination About 30 per cent of the patients will have had a previous pelvic operation These findings together with obesity, diabetes, and hypertension constitute a fair amount of pathology in addition to the primary carcinoma of the uterine body. Some of this associated pathology may distract attention from the carcinoma within the uterus and cause delay in performing a much needed curettage This is particularly true of polyps, fibroids, and adenosis.

Enough associated pathology may be uncovered to emphasize the need for a complete general physical examination in every patient suspected of having carcinoma of the endometrium.

Local examination may at times be inconclusive largely because of obesity. Palpation of the abdominal wall may reveal the presence of a mass rising above the symphysis It may, of course, represent the end stages of carcinomatous infiltration, with a markedly enlarged uterus On the other hand, a large irregular fibroid uterus may harbor an early carcinoma of the endometrium Hematometrium or pyometrium may be of appreciable size and easily palpable abdominally. Chisholm reported an enormous hematometra secondary to carcinoma of the fundus, which rose to within 2 inches of the xiphoid and contained 14 pints of bloody fluid.

Examination of Cervix

Vaginal palpation and inspection are of extreme importance Careful inspection and biopsy of the cervix are almost diagnostic "musts," because the disease may have extended down from the fundus to involve the cervix and because all the symptoms believed to be caused by carcinoma of the body may come from an endocervical epidermoid carcinoma of the cervix. Carcinoma of the cervix is commonly regarded as a disease occurring in the premenopausal age, and certainly the peak incidence comes at this time. It is so much more common than carcinoma of the fundus, however, that at about the age of 70, the peak incidence for carcinoma of the fundus, the two are present in equal frequency. Inspection of the cervix may reveal blood coming from the uterine canal or even fragments of tissue extending from the external os.

Examination of Vagina

Complete inspection and palpation of the vaginal canal are essential Nodules may appear, either as fungating areas or without break in the vaginal mucosa, anywhere in the entire vaginal tract. Likewise it is important to observe the vaginal mucous membrane itself. Randall has stated that carcinoma of the fundus does not appear where there is evidence of atrophy of the vaginal mucosa, and,

PLAN OF TREATMENT

Scheffey follows a definite plan of therapy where abnormal uterine bleeding is encountered in a woman over the age of 40 who is believed to have fibroids within the uterus.

(1) Diagnostic curettage with radium available.
(2) Biopsy of both the cervix and endocervical canal.

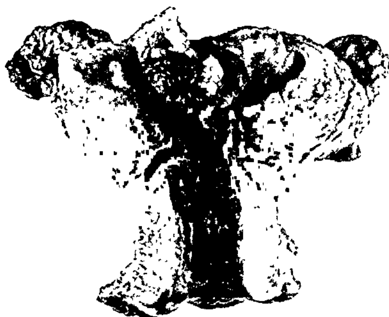


FIG 11 —Adenocarcinoma, grade II, arising at the cornua, this is frequently missed at curettage.

(3) If no submucous tumor is present or the uterus is not enlarged, 50 to 100 mg. of radium are given.
(4) If the four-hour pathologic report is benign a small dose of radium is given.
(5) If cancer is found within the uterine fundus, a full dose of radium is administered.
(6) If the uterus is enlarged, the uterine canal irregular, or adnexal disease is present, total hysterectomy is indicated.
(7) When hysterectomy is performed the uterus should be opened at the operating table. The presence of carcinoma calls for the removal of the adnexa.

Meigs would caution the surgeon that if doubt exists about the final diagnosis, the part of wisdom is to wait for the permanent sections.

ACCURACY OF CURETTAGE

Norris and Dunne, commenting on the accuracy of the diagnosis of carcinoma by diagnostic curettage, note that in fully one-third of the cases carcinoma was

(c) the uterus may be enlarged or not, but there is extension to the cervix and possible invasion of the vagina,

4. The uterus is enlarged and fixed with evidence of extrapelvic metastases

OTHER MODIFICATIONS

Miller builds his classification on the size of the uterus in relation to the development of the uterus in different months of pregnancy

Inasmuch as the diagnosis cannot be definitely made in most cases until curettage is done, Ward introduces a practical note in that the depth of the uterine cavity is considered in relation to Fricke's classification This is particularly valuable when intra-uterine radon is to be given either as definitive treatment or as a preliminary to subsequent surgery This still gives no indication of the size of the cavity except for its depth, nor does it consider that a small carcinoma may develop high up in a cavity enlarged by concomitant fibroids. Nevertheless, Healey, Miller, and others have shown that a better prognosis is by and large obtained in the small and normal-sized uterus.

The classification on the basis of the size of the uterus should continue to be employed, but whether it should dictate the type of treatment, except in obviously advanced disease, is debatable.

DIAGNOSIS

GENERAL COMMENT

Inasmuch as not all carcinomas of the endometrium occur in the postmenopausal age group, it is important to keep in mind that any abnormal uterine bleeding may have a malignant source in the uterus regardless of the age at which it makes its appearance. Carcinomas of both endometrium and cervix have made themselves manifest at an early age Hirst reported the removal of a cervical polyp in an obese girl of 16 because of profuse bleeding The curettage was repeated five months later and the base of the polyp fulgurated. Eleven months thereafter a soft friable mass extended from the external os although its base was within the uterus This proved to be frank cancer associated with a markedly hyperplastic endometrium in the remaining portions of the uterine cavity Norris and Vogt reported similar findings in a girl of 24 with a history of a previous curettage five years earlier.

Actually the incidence of carcinoma of the body of the uterus within the reproductive age varies between 25 and 35 per cent Inasmuch as carcinoma of the cervix has its peak incidence during the same period of time, the possibility of malignant disease must be kept in mind when any gynecologic operation is contemplated If the surgeon will make it a definite rule, without exception, to perform a curettage and thorough cervical biopsy in every operative case, the tragedies incident to a mistaken diagnosis will be materially reduced. It would also be worthwhile at this point to caution the physician against the indiscriminate use of hormones and roentgenologic treatment in this age group without first performing a diagnostic curettage This is a common and regrettable practice The same may be said for the use of radium given to control abnormal bleeding on the suspicion that the bleeding is functional or due to fibroids.

It is interesting to observe how closely Meigs' experience from the Massachusetts General Clinic parallels that of Telinde at Johns Hopkins concerning the explanation of postmenopausal bleeding.

	Meigs (MGH)	*Telinde* (Johns Hopkins)
Due to cancer of the cervix	40 per cent	32 per cent
Due to cancer of the fundus	20 per cent	15 per cent
Due to other causes	40 per cent	53 per cent (3 per cent Cancer of Ovary)

Thus there is an even chance that the cause of postmenopausal bleeding will be found in the reproductive tract.

When To Do Curettage

Inasmuch as Taylor found several instances of late development of carcinoma after a previous curettage, one after 16 years, he is of the opinion that it is important to regard a single instance of vaginal bleeding as significant enough to call for investigation. It is impossible to place a time element on it. Ewing observed that the progression rate of the disease varies so that early recognition is difficult. Waldstein finds that the cases of endometrial carcinoma fall into 2 groups. If they are observed during the first year they tend to be localized and operable; beyond that period they are advanced and inoperable.

It is, therefore, important to make a diagnosis early. Curettage can hardly be avoided, for it is the sole means of any accuracy at hand by which a diagnosis can be made, yet Miller found that 72 per cent of his series with a history of postmenopausal bleeding had never had a curettage. This was also true in 65 per cent of the premenopausal group Scheffey had the same experience. Perhaps this does not represent neglect, but medical schools have taught for years that postmenopausal bleeding should be regarded as due to carcinoma of the uterus until proved otherwise.

Endometrial Biopsy

It is often possible to make a diagnosis of carcinoma of the endometrium at the time of the office examination The endometrial biopsy should be regarded as a substitute for diagnostic curettage. A positive specimen is a definite finding but a negative report means only that no malignancy was discovered in that material.

Vaginal Smear

The same observation may be made for the vaginal or Papanicolaou smear. The reports have less accuracy than for carcinoma of the cervix. A diagnostic error of 26 5 per cent was noted by Graham among 113 cases of cancer of the endometrium It is fair to point out that these figures are based on the secretions from the vaginal pool. This method was chosen on the theory that some simple method should be devised that did not require special instruments or experience and could easily be followed by the general practitioner. Where smears are taken by a suction apparatus, as suggested by Bourgeois and Cary, the accuracy is much

not recognized prior to the operation, and in 15 per cent it was totally unsuspected. This was particularly true where fibroids were found in association with intra-uterine cancer. The same may be said for uterine polypi. This tendency to regard abnormal bleeding before the menopause as due to fibroids occurs continually In recent months an obese woman of 48 entered the hospital as an emergency because of a massive hemorrhage associated with excruciating cramp-like uterine pain. Examination revealed a markedly dilated cervix and an orange-



FIG 12 —Endometrial polyp (benign) arising at the cornua

sized prolapse of a submucous fibroid. At curettage carcinoma was found in the uterine fundus.

CURETTAGE IN POSTCLIMACTERIC PERIOD

In the postmenopausal era there can be no question that curettage is indicated when vaginal staining, spotting, or sudden gushing appear after any appreciable period of amenorrhea. Many cases go undiagnosed for months because of the failure to appreciate the significance of this symptom. Many physicians reassure the patient that menstrual function has returned which the patient is pleased to believe

Sampson, because of the possibility of the spread of malignancy through the tube, believes that curettage may be harmful, but there is some evidence by LeClerc and others that the tubes may be closed in the postmenopausal group where carcinoma is found. Moreover, all postmenopausal bleeding is not due to carcinoma However, the fact that 50 per cent of postmenopausal bleeding is due to uterine cancer is sufficient to regard such a history as suspicious of malignancy.

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Vaginal Smear

The same observation may be made for the vaginal or Papanicolaou smear. The reports have less accuracy than for carcinoma of the cervix. A diagnostic error of 26.5 per cent was noted by Graham among 113 cases of cancer of the endometrium It is fair to point out that these figures are based on the secretions from the vaginal pool. This method was chosen on the theory that some simple method should be devised that did not require special instruments or experience and could easily be followed by the general practitioner. Where smears are taken by a suction apparatus, as suggested by Bourgeois and Cary, the accuracy is much

not recognized prior to the operation, and in 15 per cent it was totally unsuspected. This was particularly true where fibroids were found in association with intra-uterine cancer. The same may be said for uterine polypi. This tendency to regard abnormal bleeding before the menopause as due to fibroids occurs continually. In recent months an obese woman of 48 entered the hospital as an emergency because of a massive hemorrhage associated with excruciating cramp-like uterine pain. Examination revealed a markedly dilated cervix and an orange-



Fig 12—Endometrial polyp (benign) arising at the cornua

sized prolapse of a submucous fibroid At curettage carcinoma was found in the uterine fundus

Curettage in Postclimacteric Period

In the postmenopausal era there can be no question that curettage is indicated when vaginal staining, spotting, or sudden gushing appear after any appreciable period of amenorrhea Many cases go undiagnosed for months because of the failure to appreciate the significance of this symptom. Many physicians reassure the patient that menstrual function has returned which the patient is pleased to believe.

Sampson, because of the possibility of the spread of malignancy through the tube, believes that curettage may be harmful, but there is some evidence by LeClerc and others that the tubes may be closed in the postmenopausal group where carcinoma is found Moreover, all postmenopausal bleeding is not due to carcinoma However, the fact that 50 per cent of postmenopausal bleeding is due to uterine cancer is sufficient to regard such a history as suspicious of malignancy.

carcinoma. Where the curettings are polypoid in type, however, the strips may break up, and when the finger is run over them they break up and dissolve much as does carcinoma. In this instance, only the microscope can make the diagnosis which even then may be open to question.

Cure by Curettage. Vogt found 22 cases reported in the literature where the cancer of the endometrium was believed to be cured by curettage. Such cases are beginning to appear in the literature, particularly where there has been a history of prolonged estrogen therapy. Perhaps these cases belong with the 44 cases studied by Novak, where the diagnosis of carcinoma of the endometrium was greeted with some skepticism. The corollary to this, however, is the report by Taylor that 19 per cent of 152 cases of carcinoma had had at least one curettage prior to admission to the hospital for cancer. Carcinoma was in all probability present at the time of the first curettage.

Frozen Section. The problem in the postmenopausal group is not so difficult provided the curettage is complete. Where the present trend of preoperative radiation is in vogue, the diagnosis must be made on the frozen section of tissue removed at the time of curettage The diagnosis may often be made on the gross appearance of the curetted tissue which is usually white or colorless, crumbling, granular, and hard. Where doubt exists, it is better not to rely completely on the frozen section but to wait for the permanent paraffin section Radium therapy as a preliminary step to subsequent surgery or as definitive treatment follows the report of the frozen section

The greatest element of doubt in grossly carcinomatous curettings comes in the differential diagnosis of adenocarcinoma versus adeno-acanthoma. This is an extremely difficult decision when based on frozen section examination. Inasmuch as adeno-acanthoma is resistant to radiation, permanent sections are desirable. As a clinical note, it is suggested that the gloved finger will detect a greater resistance to the adeno-acanthoma, with less tendency to disintegrate than is encountered with adenocarcinoma.

Clinical Observation The Clark test for carcinoma of the fundus has stood the test of time and may be a helpful adjunct to curettage This depends on the observation of profuse bleeding from the canal when the uterine probe is withdrawn.

Sampson has pointed out one danger of curettage in that through manipulation carcinomatous tissue may be forced through the tube to be implanted on the ovary or peritoneum Gentle curettage is, therefore, indicated to overcome this danger and to prevent perforation of the uterus either by dilators or curette. Where perforation is known to have occurred, the surgeon need not be stampeded into performing an immediate hysterectomy for this reason alone. It is well, however, to discontinue the curettage. Radium should never be given at this time.

The curettage should be methodical and complete. Every surgeon has had the experience of missing a carcinoma lurking in the cornua of the uterus. A flat polypoid growth may also be overlooked when it occurs at the top of the fundus. It is an excellent practice to follow the curettage by exploration of the uterine cavity with a common duct forceps in order to pick up an occasional polypoid growth which has rolled away from the curette

Evaluation of Cavity Inasmuch as we are asked to determine radium in can-

greater. The same point of view should be extended to the vaginal smear that one employs in the biopsy reports A positive smear should be regarded as significant, a negative finding means nothing

LOCALIZATION BY LIPIODOL

Inasmuch as radiation therapy both as an adjunct to surgery and as a complete treatment is considerably handicapped by the inability to localize the carcinomatous area within the uterus by other than diagnostic curettage, it has been suggested by LeClerc that roentgenographic localization is possible through the injection of the radiopaque medium, lipiodol, into the uterine cavity. Recently Kaplan has adopted this method as a preliminary to the insertion of a newer type of intracavitary radium applicator The disadvantages are obvious if Sampson's observations are correct, that malignant epithelium may be forced through the tubal ostia into the peritoneal cavity. All authors stress gentleness in the manipulation incident to curettage in order that disease may not be forced into the lymphatics. LeClerc believes as the result of a considerable series of lipiodol studies on this type of patient that the tubes of patients in the postmenopausal group are not patent No pressure is exerted, of course, and just enough dye is injected to outline the uterine cavity The advantages of the procedure are obvious The diagnosis must still be made by curettage but the localization of the tumor is of great importance if any reliance is to be placed on radiation therapy

THE CURETTAGE

Because of a variety of etiologic causes existing prior to the menopause the presence of abundant curettings has less diagnostic significance than the same findings after the menopause. The curettings should be carefully examined by running the finger over them gently It is well to collect the products on moist, fine meshed gauze lest the material become entangled in the coarse interspaces. Should the particles appear in chunks, showing evidence of necrosis, the *products of conception* may be suspected Organized blood clot suggests retained membranes

Polypi often are dislodged intact and are easily recognizable. They are found about eight times as frequently in the carcinomatous as in the normal uterus Rarely are they confused with carcinomas for polypi tend to have a definite form and are by and large firm, pink, and smooth compared to the whitish crumbling curettings of carcinoma The confusion may arise from associated hyperplasia

Hyperplasia itself, particularly in the reproductive period, is the most confusing, frequently calling for the highest degree of acumen in order to differentiate it from carcinoma Here there is a real possibility of error As Novak observes, marked proliferation, with an extreme adenoma-like pattern and active stroma, coupled with stratification of the epithelium, so closely resembles carcinoma that it is the part of wisdom to err on the side of hysterectomy rather than take the chance of causing a tragedy by further observation of the case. This is especially true where hormone therapy has entered to cloud the histologic picture

Gross Examination In gross the curettings are abundant and usually come away in long strips which are smooth, firm, and pink, not easily confused with

As a final word of caution it would be well to stress the fact that (a) where there is any doubt it is better to err on the diagnosis of malignancy, hence the remark of the eminent pathologist, Meyer, quoted by Novak, "Nicht Carcinoma besser heraus." (b) Where the final conclusion is reached that the tissue is benign and observation is to be the course for the future, it is *important to regard*



FIG 14.—Fibroid at the cornua No carcinoma, but distortion of the canal is evident. Uniform radiation distribution is impossible.

any future bleeding as a violent danger signal calling for treatment at once. In too many instances such bleeding has been ignored because of a previous negative curettage, the more recent the more dangerous.

DIFFERENTIAL DIAGNOSIS

The predominant symptom suggesting the possibility of the presence of adenocarcinoma of the uterine body is, of course, bleeding. The diagnosis, therefore, becomes complicated by the variety of causes for abnormal uterine bleeding which appears to have a predilection for the same age period in which carcinoma is so frequently found. Except for an irregular menstrual pattern and a delayed menopause there is little in the history to differentiate carcinoma from any of the other causes of menstrual disturbance, and these findings are suggestive not pathognomonic. Unless the disease extrudes from the cervical

cerocidal doses to a carcinoma we cannot see, it is important to gain as complete a knowledge of the size and contour of the uterine cavity as possible. Not infrequently the uterine cavity is found to be distorted by the presence of a totally unsuspected submucous fibroid which militates against the proper application of radium and may argue for immediate hysterectomy. Usually, if the minimal bleeding is due to fibroids or causes other than carcinoma, the curettings will be scanty in amount, unless they are complicated by hyperplasia. While the cervix



Fig 13—Extensive uterine cavity, huge fibroid Localized carcinoma at one cornua. This demonstrates the difficulty of uniform radiation and the likelihood of misdiagnosis through failure of interpretation of bleeding source.

is often found to be open and the canal deeper and more irregular in the presence of a submucous fibroid, it must also be borne in mind that the two not infrequently coexist and the curet may have difficulty in dislodging carcinoma which is hidden in the cornua above a submucous fibroid

Clinical Suggestions In order to avoid mistakes in diagnosis following a curettage, Taylor suggests that.

(1) All curetted material, however small, be saved for histologic examination
(2) An incomplete curettage is not enough, for a small carcinoma, particularly at the cornua, may be overlooked
(3) In a suspicious case single pathologic sections are not enough, for the microtome may pass over the particular portion containing the carcinoma.
(4) In certain types of histology the differentiation is so highly controversial that multiple serial sections may be required before a definite diagnosis can be made.

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canal or implants appear on the vaginal vault, the physical examination is unlikely to give any working clue to the diagnosis of endometrial carcinoma.

RECOGNITION OF DISEASE

The disease is usually recognized in one of three ways: (1) upon the gross findings of tissue removed at curettage and confirmed on frozen section, (2) upon immediate examination of the uterine cavity of a uterus removed at operation, and (3) upon the late reports of permanent pathologic sections of the extirpated uterus. Only one of these sources, the curettage, permits a properly planned attack upon the malignancy The others are concerned with how to salvage as much as possible from a procedure carried out without complete information.

It is thus important to keep uppermost in our minds the fact that abnormal uterine bleeding both before and after the menopause may be due to carcinoma until this diagnosis is properly excluded. If we consider the possibility, fewer tragedies will result, for example, from the discovery of a totally unsuspected carcinoma in a patient who has been carried along on hormone therapy without a definite preliminary diagnosis.

TREATMENT WITHOUT CURETTAGE

More attention should be paid to the admonitions of those familiar with the disease that without such a diagnostic procedure, hormone therapy should be used sparingly, if at all, in this premenopausal age group, particularly if there is any reason to suspect, from the family history for example, that carcinoma might be induced by its use. Likewise too much roentgen therapy is given for abnormal bleedings without the benefit of a preliminary curettage. Surgeons have long recognized that it is wise to have any uterus removed at operation examined at the table before the abdomen is closed, but too few make it a routine practice

Attention is called to these observations because uterine malignancy is too frequently uncovered accidentally Before considering the differential diagnosis of abnormal uterine bleeding we must first consider the possibility of malignancy of the uterus.

ABNORMAL BLEEDING

Carcinoma of Cervix It is impossible to discuss the causes of abnormal uterine bleeding in relation to endometrial carcinoma without first ruling out the cervix as a source It has been shown that carcinoma of the cervix occurs approximately eight times more frequently than fundal carcinoma The proliferative lesions of the cervix are fairly obvious, and such diagnostic aids as the vaginal smear and biopsy confirm the diagnosis But not all carcinomas of the cervix manifest themselves externally Some will arise within the endocervix and be unsuspected on direct inspection Curettage and biopsy of the endocervix are, therefore, imperative in the face of unexplained uterine bleeding.

While we keep firmly in mind that abnormal uterine bleeding may be due to carcinoma, it is obvious that malignancy as a cause will be found infrequently even after the menopause. Gardner has evolved a working outline for the

consideration of the etiology of uterine bleeding. It is assumed that bleeding is coming from the uterine canal and that carcinoma of the cervix has been excluded.

Functional Bleeding. Among the medical causes of abnormal uterine bleeding the various forms of metropathia hemorrhagica are legion. An improper balance between estrogen and progestin secretion may result in the persistence of a proliferative phase of the endometrium or frank hyperplasia. These patients bleed irregularly and often persistently.

Another form of endocrine imbalance can be traced to a disturbed thyroid function. A truly myxedematous patient will in all probability have amenorrhea, but where the basal metabolic rate, confirmed by cholesterol determinations, is found in ranges from −15 to −40, bleeding is apt to be profuse at the time of the period

Though bleeding from the nasal mucous membrane and gastro-intestinal tract may indicate the possibility of diseases of the blood-forming organs such as thrombocytopenic purpura and acute leukemia, it is well to remember that vaginal bleeding may be the first symptom Examination of the blood smear may serve to establish the diagnosis, provided the patient is not in a remission.

Inflammatory adnexal pathology may be sufficient to stimulate the ovary to abnormal function and thus produce abnormal uterine bleeding. Where such bleeding occurs, tubo-ovarian abscesses are not infrequently present and may be recognized on pelvic and rectal examination. The uterus is generally fixed and the outlines of the uterus and adnexa obscured.

Tumors of the ovary, both benign and malignant, frequently produce uterine bleeding either through indirect effect on the endometrium as noted when fibroma, theca- or granulosa-cell tumors are present, or by producing actual metastases to the endometrium from a primary carcinoma in the ovary. Three per cent of the postmenopausal bleeding in Telinde's series was due to ovarian carcinoma The coexistence of carcinoma of the endometrium and theca-cell or granulosa-cell carcinoma has already been commented upon.

A diagnosis may be suspected if adnexal masses are palpable but frequently they are small Banner and Dockerty found that they were rarely larger than 12 cm and may be as small as 3 cm. with an average of 6 cm. Smith and Hertig note the presence of cortical granulomas responsible for uterine bleeding within a normal sized ovary. Because the uterus is commonly enlarged it may not be possible to distinguish uterine from adnexal enlargement.

Complications of Pregnancy Such complications are rare in the early reproductive period but are not infrequent as the menopause is approached. A threatened or incomplete abortion may simulate carcinoma of the endometrium in that the uterus is enlarged and the cervix patulous, soft, and boggy. Examination of extruded particles or the findings on endometrial biopsy may be enough to establish the diagnosis, but frequently curettage and microscopic section are necessary. The same may be said for ectopic pregnancy. Fortunately ectopic pregnancy in women close to the menopause is a rare finding, but conversely carcinoma of the endometrium may be present in the thirties.

While hydatiform and chorio-epithelioma are rare they do exist and may produce prolonged and protracted uterine bleeding. The uterus is enlarged

and often irregular with frequent and appreciable enlargement of the adnexa. Chorionepithelioma may develop following a mole, incomplete abortion, or more often a normal pregnancy. Gardner points out that curettings are often misleading in attempting to differentiate a hydatid mole from a chorionepithelioma. In many instances examination of the uterine wall is necessary. Again both of these entities are rarely found in the immediate climacteric period, but carcinoma of the endometrium may occur early. As an example, six years ago a 36-year old woman had had a pregnancy complicated by a mole. Two subsequent normal deliveries followed, but during the last eight months before a supravaginal hysterectomy was done for an irregular fibroid uterus, a choriocarcinoma was found unexpectedly in what appeared grossly to be a fibroid uterus. This will serve to illustrate the value of opening every extirpated uterus at the operating table. Not having done so, the surgeon is faced with the problem of the proper management of the retained cervix and ovaries.

Benign and Malignant Tumors of the Uterus. Adenomyosis produces an enlargement of the uterus with attendant fixation of the broad and uterosacral ligament, particularly if the external form of endometriosis accompanies the intra-uterine growth Dysmenorrhea that continues throughout the menstrual period is a helpful diagnostic symptom. Inasmuch as hyperplasia, adenomyosis, and cancer have the property to invade muscle, adenomyosis has been advanced as an etiologic factor in endometrial cancer With the associated hyperplasia, bleeding is frequently profuse and prolonged

Submucous fibroids are prone to produce a type of bleeding which is both profuse and gushing in character, findings commonly observed with carcinoma. Novak finds that the cervical canal is not uncommonly patulous in the presence of a submucous fibroid

Other fibroids do not of themselves produce bleeding, rather they may be produced by the same source that gives rise to the endometrial hyperplasia or other stimulated uterine epithelium, which in time does bleed and often profusely and protractedly The pitfall in diagnosis is to consider the symptom as due to the fibroid. This is particularly true after the menopause unless the tumor is pedunculated and necrotic It is far healthier to consider that the bleeding is secondary to a coexistent carcinoma or sarcoma The same may be said for uterine polyps.

Sarcoma of the uterus is found only rarely, in perhaps a frequency of 2 per cent of all malignant tumors of the uterus If carcinoma of the cervix appears eight times more often than carcinoma of the endometrium, then the latter is about eight times as common as sarcoma From its history and physical appearance the differential diagnosis between sarcoma and carcinoma may be impossible. The uterus is frequently enlarged and soft and is often confused with pregnancy or a degenerating fibroid. The differential diagnosis from carcinoma depends on the microscope.

Other Causes. Following injury to the cervical canal, and often in the climacteric period, stenosis of the uterine canal produces a pyometra or hema-

ith cramps and a gushing type of uterine

and malodorous. Previous intra-uterine

oduces this type of pathology. Particularly

in the postclimacteric period the two may coexist with carcinoma of the endometrium.

Tuberculosis of the endometrium may produce irregular profuse vaginal bleeding even in the age of the menopause and the symptoms may be mistaken for carcinoma. Whereas it is commonly found in association with tuberculous involvement of the tubes, it may appear as isolated pathology within the endometrium.

Hormonal therapy is in such widespread usage that constantly recurring confusion in differential diagnosis is rampant. Bleeding occurs both from withdrawal of the drug as well as its prolonged administration. The altered histologic pattern is so variable following estrogen administration that experienced pathologists are frequently at a loss to make a diagnosis. Hysterectomy following uncertain pathologic opinion is not uncommon. In defense it is better surgical judgment to err on the side of removal.

GROSS PATHOLOGY

Types

Inasmuch as the uterine cavity is lined by mucous membrane made up of simple columnar type of epithelium containing numerous glands that extend more or less deeply into the musculature, it is not surprising that carcinoma of the endometrium may arise anywhere within the uterine cavity. It arises as a rule where the endometrial lining is thickest, namely, at the top or fundus of the uterus and usually at one cornua, but it may arise just above the internal os. The disease may originate in one of two ways: It may appear as a solitary area which may then remain local or spread over the rest of the uterine cavity or it may arise primarily over a wide area.

Circumscribed. In all probability carcinoma of the endometrium arises in a sharply circumscribed area at least during its early phases. The first indication, according to Ewing, appears as a slight thickening of the mucosa in one area. Slowly the growth enlarges toward the uterine cavity with a tendency to form papillary or polypoid projections which may be sharply demarcated from the rest of the mucosa Grossly they appear as flat velvety lesions which have a tendency to be pedunculated It is this sort of lesion that is removed at the time of curettage and found to be the only site of malignancy in the entire hysterectomized uterus. Obviously a cure would not be accomplished by curettage, but removal of the uterus will certainly eradicate the disease. One may question the pathologic interpretation of the specimens from curettage in such instances, but Novak collected 85 authenticated cases from the literature where such polypoid growths were proved to be the only areas of cancer in the removed uterus. It serves to emphasize the localized nature of the tumor. There is a tendency to consider carcinoma of the endometrium as a single disease entity which it obviously is not. This fact is emphasized from the nature of the growth from this small beginning As the circumscribed tumor grows, it commonly continues to extend into the uterine cavity to become a large bulky growth which may even distend the cavity. On the other hand, the disease in its normal progression, instead of expanding into the general uterine cavity,

may invade the musculature early, extending along the vessels to the serosa, as reported by Ewing The actual presenting tumor may be small This type of extension may be found within an adenomyoma, giving rise to diffuse infiltration throughout the muscle wall while the endometrium demonstrates only moderate involvement The fact that these foci may be multiple within the



FIG 15 —Extensive papillary outgrowth filling the cavity without involving the musculature

same uterus lends background to the impression that many carcinomas of the fundus arise from sharply localized areas.

Diffuse While many adenocarcinomas remain local even in the advanced stages of the disease, others spread to involve a wide area or at times the entire inner cavity. It is hard to know whether spread has taken place from a point source or whether the lesion arose simultaneously throughout the mucosal lining Heurlin, quoted by Ewing, found the diffuse type of tumor to be about twice as common as the circumscribed form. About 50 per cent will show more than one-half of the entire mucosa involved in disease.

Grossly one encounters a markedly thickened endometrium with irregularly placed polypoid areas of varying sizes There is a marked tendency to superficial ulceration and often frank necrosis as though the disease had outgrown its blood supply. Again, as in the circumscribed type, extensive surface involvement may be noted with little invasion of the underlying musculature. Con-

versely, broad areas of invasion may be encountered, varying in depth of penetration, but often reaching the serosa of the peritoneal covering. In such cases the uterus becomes diffusely enlarged up to two or three times its normal size. In the absence of fibroids the uterus remains symmetrically enlarged until subserous invasion by tumor is encountered. These may appear beneath the serosa as firm white nodules. Rupture may take place with dissemination of cancer cells throughout the pelvic peritoneum.

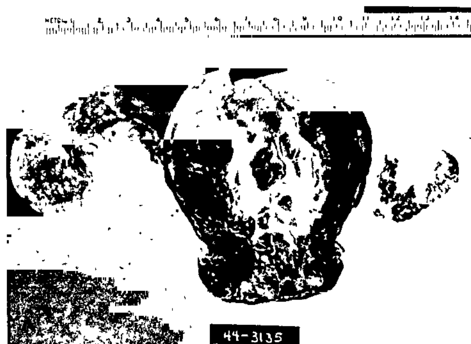


FIG 16—Extensive superficial growth involving the entire cavity, including the endocervix

MANNER OF SPREAD

In this manner the disease tends to involve adjacent structures such as the bladder and rectum, leading to the extreme manifestations of bladder and rectal fistula formation. Extension of the disease beyond the uterus other than by direct invasion takes place rather late in the disease and generally occurs through the following five channels.

(1) Lymphatics
(2) Fallopian tubes
(3) Blood stream
(4) Surface implantation
(5) Peritoneal cavity

As long as the disease remains confined to the cavity itself there is little tendency to involve the lymphatics, but as soon as the muscle becomes invaded or the tumor has reached the peritoneum, lymphatic penetration is likely. The extension is slow compared with that encountered in cervical carcinoma. Randall believes that the discrepancy lies in the different lymphatic drainage as much as in the growth potential of the individual tumor. Before proceeding with

a discussion of the natural spread of the disease one should review the lymphatic drainage of the uterus.

Lymphatic Drainage. Within the uterus, lymphatics are found running from the endometrium horizontally to communicate with a longitudinal network extending from the fundus of the uterus to the cervix. These in turn drain into collecting channels which form along the lateral sides of the uterus beneath the serosa. Dissemination then may follow several channels. Extension commonly takes place along the upper portion of the broad ligament where free anastomosis takes place between the tube and the hilum of the ovary, before proceeding to the pre- and lateral aortic nodes on the left and the pre- and lateral caval nodes on the right, and thence to the kidney area. It is possible that the penetration may take place into the channel of the lymphatics following the course of the round ligament to involve the superficial inguinal nodes. This communication is less rich in anastomotic branches, and the common method of spread follows the main channel in the upper broad ligament. It is thus obvious that the route chosen for extension depends for the most part on the site and extent of the tumor within the uterus. Thus cancer developing, as it most frequently does, at the fundus of the uterus, will follow the above method of spread. Where the disease arises in the central portion of the body of the uterus, the extension in all probability will be to the transverse ramification of the lymphatic bed to follow the course of the ureter and uterine vessels and involve the ureteral, iliac, obturator, and hypogastric nodes. Intercommunication takes place with the lymphatics of the cervix and vagina, with free exchange with the channels found around the bladder and rectum. Thus a growth situated in the lower portions of the uterus may be expected to follow the same pathway in its lymphatic spread as cervical carcinoma does, but with considerably less readiness. Carcinoma arising on the posterior portion of the body of the uterus may extend into the posterior plexus coursing along the uterosacral ligaments to communicate with the rectal lymphatics and hence to the promontory of the sacrum.

Involvement of Parametrium. Once carcinoma has involved the lymphatics and spread beyond the confines of the uterine cavity, a new stage in the disease has been reached. The parametrium then becomes involved, either by direct extension of the growth on one or both sides, or by the lymphatic pathways outlined. When this will take place depends on the type of tumor and its location within the uterus. Parametrial fixation does not of itself mean invasion by tumor, for it may be thickened where no disease is present. Necrosis of the tumor within the uterus may produce an inflammatory reaction within the lymphatics and nodes of the parametrium which may simulate malignant involvement. On the other hand, Ewing has found the parametria to be invaded by cancer in the fine lymphatics without involving nodes. Thus the parametria may serve as a check on the disease. A widespread surgical removal of the parametria should, therefore, improve the prognosis.

When the main lymphatic channels are reached, and this usually occurs late in the course of the disease, metastases may be expected to extend to regional nodes and more distantly to lung, liver, and bone.

There is a striking tendency, however, for the disease to remain local without

extension to the nodes, even in the face of extensive local malignancy. Ewing, from observations of postmortem specimens, found the regional nodes to be free of disease in 66 per cent of the fatal cases.

Involvement of Cervix and Vagina. The possibility of retrograde lymphatic spread to the cervix and vaginal mucosa cannot be overlooked. Involvement of the cervix may take place by direct extension through the cervical canal to present at the external os as a friable polypoid growth often confused with an endometrial polyp. Novak has observed that benign polypoid hyperplasia restricts itself to the area above the internal os, but carcinoma knows no such physiologic barrier. The cervix and vaginal mucosa also become involved by lymphatic extension. Carcinoma of the endometrium is not infrequently a disease of the entire uterus and this fact supports the contention that supravaginal hysterectomy has no place in the treatment of cancer of the uterine fundus. Involvement of the vaginal mucosa, while commonly found at the fornix of the vagina, may appear at single or multiple isolated spots in the lower vaginal canal, which suggests retrograde lymphatic spread rather than implant metastases. Such metastases are not infrequently found around the urethra and may appear as the first indication of the disease. Meigs found 12 per cent with vaginal metastases among 206 cases of endometrial cancer. This conforms to Strachen's observations from England where 12 such instances were found among 90 cases Smith found 6.3 per cent among 365 cases with a strikingly similar figure of 5 5 per cent after treatment by radium. All agree that such manifestations indicate advanced disease with a definitely poor prognosis. Many writers have considered such metastases as surface implants, but Wallis voices the opinion of most authors when he doubts whether such grafting of tumor on the vaginal surface ever occurs Meigs agrees that these metastases are without question secondary to lymphatic infiltration rather than surface plants, but adds a note of caution as to injudicious handling of the uterus during operation, lest tumor particles be squeezed into the lymphatics or forced from the uterine cavity to become implanted upon fresh raw surfaces at the operative site.

Spread by Fallopian Tube. Willis and Sampson stress the need for extreme gentleness in manipulation of the uterus at the time of pelvic examination, curettage, and hysterectomy for another reason, namely, that tumor particles may be forced into the lumen of the tube to become implanted on the ovary or peritoneum. Sampson felt so strongly about the possibility that for some period of time he advised that no curettage be done. This point of view was abandoned when it was realized that accurate diagnosis could not be expected without a curettage, but Sampson continued to advise, as do others, that the tubes be ligated as the first intra-abdominal step in removal of the uterus. Willis believed that in the reproductive period uterine contractions forced into the tubal lumen tumor particles which the cilia of the tubal epithelium were not strong enough to resist This was particularly true if for one reason or another the cervical os was occluded or retroversion was present Forceful manipulation at the time of curettage or surgical removal would be contributory.

There appears to be little doubt in Sampson's mind and in the minds of many foreign observers that cancer cells may be found lying free in the tubal lumen in the presence of adenocarcinoma of the endometrium without the presence

of malignancy within the tube itself or in the lymphatics leading to it. Reichel first reported such findings in 1888 with confirmation forthcoming from V. Frague, Sitzenfrey, and later from Sampson and from Offut Wallis quotes 3 instances where such implants were found on the ovary where muscle invasion was minimal and no lymphatic penetration noted in the broad ligament and mesovarium. Offut suggests that such a routine of dissemination is possible, for out of 53 cases selected from the Mayo Clinic records for intensive study, 15 showed secondary involvement of the tubes with cancer cells in the lumen where the lymphatic and blood vessel channels were normal.

Randall believes that spread in this manner is possible but of little importance, for early metastases may be found deep in the ovary. Such metastases often have a good prognosis Novak finds the majority of tubal metastases to be submucosal and interstitial. Arguing against the implant theory, he points out that even though broken off tumor cells are found within the tubal lumen there is no evidence that such particles implant as cancer.

It is, therefore, more reasonable to assume that cancer of the endometrium, like carcinoma elsewhere, extends by proliferation of tumor cells within or by permeation along the lymphatics The spread, of course, could take place secondary to peritoneal involvement and thence to the ovary but such implants are found without involvement of the pelvic peritoneum or even of the serosa of the uterus If the spread to the ovary were by the blood stream, a higher percentage of ovarian involvement would be encountered with carcinoma of the endometrium. Such extensions are rare. Novak could find but 7 among 147 cases, and Norris and Vogt 2 among 115 cases of fundal cancer. Lynch and Dockerty found that 4 per cent of the cases operated upon for cancer of the endometrium had one or both ovaries involved with cancer. Actually this is much less than one would anticipate in view of the free anastomosis among the lymphatics of the broad ligament and hilum of the ovary.

Spread by Blood Stream The possibility of the spread of the disease to the ovary by blood vessel invasion has been commented upon. It is likewise conceivable that distant metastases to lung, liver, and bone may occur in this manner. Extension to the brain has been observed without primary involvement of the lung. The explanation of this phenomenon may be due to extension through the azygous venous system to the vertebral veins as suggested by Batson Wallis believes that such a spread is of but little clinical importance, for by the time the patient has such distant metastases the diagnosis is obvious. In rare instances severe back pain has been found to be secondary to vertebral body involvement in the absence of local symptoms. Distant metastases do not invariably mean early demise, for Meigs noted one instance of a known metastasis to the liver, discovered at the time of hysterectomy, which proved to be unchanged when cholecystectomy was performed three years later. Brezina and Lindskog have reported a total pneumonectomy for discrete solitary tumor of the upper lobe of the right lung. This proved to be a late metastasis from a carcinoma of the endometrium which had been discovered years before when a total hysterectomy with removal of the adnexa had been performed. This is in keeping with the experience with malignant disease in general and is more

understandable in view of the known rate of tumor growth in cancer of the uterine cavity.

Transperitoneal Metastases. The possible mode of spread to the ovary by way of the peritoneum has been noted. It is a common clinical observation that once the disease has reached the peritoneum, progression of the fatal course of the disease is accelerated. Discrete peritoneal implants are found in over one-half of the terminal cases.



FIG. 17 —The irregular subserosal nodules are indicative of extensive invasion and lymphatic penetration

Gardiner has pointed out that it is of great importance for the surgeon to understand the natural course of the disease and its various avenues of spread, as well as to be able to recognize the gross manifestations of the disease clinically. While it is to be hoped that the disease will be diagnosed at the time of curettage, the most careful surgeon performing the most meticulous curettage may miss a carcinoma hidden in the cornua of the uterus. The pathologist continues to confront the surgeon with unexpected reports of unrecognized carcinoma.

It is, therefore, important to consider a few observations which may be helpful in making a diagnosis at the time of operation where the curettage has either not been done or is misleading.

CLINICAL AIDS

Gross Palpation. The uterus is generally two or three times the normal size and may be soft in consistency provided there are no fibroids present. This



FIG 18 —Photomicrograph of grade IV adenocarcinoma (same case as Fig 17), showing invasion of muscle

lack of firmness is in contrast to the strong fibrosis common to adenomyosis or fibroids. The wall may appear to vary in thickness. With the uterus opened, the uninvolved portions of the wall seem to be less thick. Gardner notes a color change *to a deeper red, approaching purple cyanosis, in the uterus involved* in carcinoma These observations appear simply as variations from the expected pathology and are in no way pathognomonic of endometrial carcinoma. The basic pathology can be determined only when the uterus is opened.

Opening the Uterus at Operation. Gynecologic surgeons with experience have long since adopted the routine of having every uterus opened at the operating table and its interior inspected, regardless of the preoperative diagnosis or the type of hysterectomy performed The standard procedure for carcinoma of the fundus is a total hysterectomy with removal of both adnexa. The unexpected finding of carcinoma in a totally removed uterus where the adnexa have been left and the uterus not inspected before the abdomen is closed is not as inexcusable as performing a supravaginal hysterectomy which, all will agree, should not be done in the treatment of this disease. With the uterus opened at operation, the gross appearance of the lining is usually enough to establish a diagnosis Where polypi are found or doubt exists as to the gross diagnosis, microscopic confirmation may be obtained from a frozen section

MICROSCOPIC PATHOLOGY

Precancerous Lesions

Whether or not carcinoma of the endometrium arises in a hyperplastic endometrium is debatable. The differentiation is not an easy one, for all gradations from benign hyperplasia to obviously neoplastic change are found. Moreover, the two entities may merge one into the other and have been reported as coexisting in the same endometrium. There appears to be a definite group where the pathologists differ widely in their interpretation. The difficulties in diagnosis are further enhanced where prolonged hormone therapy has been administered. What activating forces produce the hyperplasia and initiate the malignant transformation may be debatable, but the evidence for unopposed estrogen stimulation upon a sensitized uterus is strong.

Benign Hyperplasia

The etiologic relationship of hyperplasia of the endometrium and carcinoma has been discussed. Lack of agreement exists among some authors who, finding evidence of secretory activity within the epithelium, believe that the epithelium is stimulated but will not agree that it should be designated as hyperplasia The controversy then arises because of the failure to define the criteria for the diagnosis of hyperplasia.

The microscopic differentiation between carcinoma of the body of the uterus and benign gland hyperplasia of the endometrium may be difficult, particularly as the menopause approaches. In the earlier reproductive period this confusion is less likely to occur.

The gradations occur in varying degrees of proliferation from normal proliferative endometrium, mild hyperplasia, and Swiss-cheese endometrium to the markedly proliferative types that closely resemble carcinoma

Mild Hyperplasia. In this instance the changes are minimal with some tendency to form cystic glandular areas with some evidence of cyclical activity present in the cells

Swiss-Cheese Type. The typical Swiss-cheese endometrium presents varying sizes of acini lined by flat cuboidal cells showing only moderate evidence of proliferation. The chief feature of the pathologic pattern is the number of dilated cystic glands with an abundance of stroma. Further stimulation results in an increase in the amount of cystic change and the development of clusters of small glands throughout the stroma. These glands may dip into the musculature beyond the normal boundary line of the endometrium. A heaping up of epithelial cells lining the glands occurs with extensive branching of the glands. As Taylor has observed, hyperplasia and carcinoma have biologically similar properties in that a tendency to invasion is noted much as one finds in adenomyosis. On the other hand, these eccentricities on the part of endometrial hyperplasia should not be construed as evidence of malignancy. Actually Novak believes that there is little resemblance between Swiss-cheese endometrium and carcinoma, at least in the premenopausal group.

Proliferative Hyperplasia. As stimulation becomes more pronounced, the heaping up of the epithelium of the glands becomes accentuated, with a tendency

to form cysts of varying shapes and sizes, some of them small and round while others become elongated, flattened, and distorted. The nuclei may become eccentrically placed within the cell Dark-staining granules are noted and at times a nucleolus may be found Pathologists suggest that the presence of a definite nucleolus is indicative of malignant change. The epithelium itself becomes much thickened, producing crowding with the impression of many epithelial layers and the development of intraluminal papillary projections. These changes produce the confusion in the differential diagnosis from carcinoma.

Final Diagnosis. The final diagnosis must depend on (1) the irregularity of the epithelial cells, (2) the presence of abnormal nuclei, (3) the unevenness in the staining properties of the nuclei, and (4) the loss of the restorative basal membrane of the glands.

Menopausal Hyperplasia

The normal mucosa of a woman in the climacteric period will appear thin and atrophic with occasional dilated glands and rather marked fibrosis of the stroma. Wherever abnormal stimulation occurs the stroma becomes reactivated and thickened, containing dilated cystic glands with cells of the proliferative type. It is thus difficult to determine whether the response is physiologic or whether early pathology is present. Novak believes that where the glands are found to be full of an albuminoid type of transudate evidence of hyperestrinism is present. Not all are agreed, however, that different portions of the same endometrium respond in the same manner. Novak and Rutledge studied 44 cases of benign hyperplasia mistaken for carcinoma Hyperplasia differing from benign Swiss-cheese hyperplasia was noted in that there was marked disparity in the size and shape of the glands, together with abundant active stroma Varying degrees of maturity of the individual cells were noted. Such atypical hyperplasia might be found in localized areas in a field of otherwise benign hyperplasia or might be uniformly distributed throughout the endometrial lining It is these abnormal areas of proliferation that cause confusion in the differential diagnosis from carcinoma. Some authors regard such overly stimulated epithelium as an extreme degree of hyperplasia while others believe that they represent malignancy of the papillary adenomalignant type Such findings are not uncommonly observed where hormonal therapy has been given uninterruptedly. Withdrawal of estrogen therapy allows the exaggerated proliferative phase to return to normal and the confusion in diagnosis disappears.

Main Types of Carcinoma

Microscopically there appear to be three main types of carcinoma of the endometrium dependent directly upon the type of cell from which each takes origin. The papillary adenocarcinoma may be traced directly to the proliferation of the superficial cells of the surface epithelium and are therefore columnar in type. The adenomatous type of lesions, presenting gland formation, probably originates from the normal endometrial glands as the result of a stimulus from some source The line of demarcation from the surrounding normal glands is usually definite and the transition from normal to malignancy is hard to determine. The extension takes place by displacement of the normal glands,

which may occur over the entire endometrium or in isolated areas, for multiple foci of adenocarcinoma have been reported.

In addition to the main types, a combination of cell types occurs, with islands of squamous cell epithelium extending through the malignant gland pattern This pathologic picture has been called adeno-acanthoma. The frequency of its occurrence varies widely, depending upon whether the pathologist chooses



FIG. 19 —Adeno-acanthoma of uterus, showing large metaplastic plaques resembling squamous epithelium.
(Novak, E. *Gynecological and Obstetrical Pathology and Endocrine Relations*, W. B. Saunders Company, 1940)

to call any endometrium containing squamous elements adeno-acanthoma or whether the designation is determined on the basis of the predominant cell pattern Fricke found 75 per cent of 100 cases were adenocarcinoma while 11 per cent were classified as squamous. In our own series 22 per cent of adeno-acanthoma was found.

GRADING OF ENDOMETRIAL CARCINOMA

Difficulties The degree of malignancy depends upon the maturity of the cell and the extent of the differentiation from the normal. The incompletely matured or unripe cell showing little tendency to differentiate will thus be classified as the more malignant tumor.

A plan to grade the various types of malignancy would seem to be logical and reasonably simple The great stumbling block, however, occurs when it is evident that different degrees of differentiation are to be found in separate sections or even within the same section. Thus there is a tendency to grade the tumor on the basis of the predominance of the most malignant element present.

Classification. Many basically similar classifications have appeared since Kaufmann in 1911 attempted to sort out the various pathologic patterns and evolve a system of grading.

(1) Adenoma malignum
(2) Adenocarcinoma
(3) Papillary Adenocarcinoma
(4) Solid Adenocarcinoma
(5) Adenocarcinoma with squamous metaplasia



FIG 20 —Remarkable squamous metaplasia in case of adenocarcinoma (grade I) (Novak, E *Gynecological and Obstetrical Pathology and Endocrine Relations,* W B Saunders Company, 1940)

To this classification Ewing added an earlier phase of adenoma malignum called papillary adenoma malignum and a more advanced classification adenomyocarcinoma

Both Meigs and Scheffey have rightly believed that, because simple pathologic sections revealed varying grades of malignancy, a modification to a broader simpler classification would be more practical, and they have simply classified endometrial carcinoma into three stages.

(1) Papillary adenocarcinoma	=	Low
(2) Adenocarcinoma	=	Medium
(3) Solid adenocarcinoma	=	High

This latter classification has merit

MICROSCOPIC PATTERNS

Grade I or Superficial Adenoma Malignum The tumor by and large is entirely superficial, arising from the surface epithelium as a papillary type of growth



Fig 21.—Photomicrograph of papillary adenocarcinoma of the body of the uterus, low grade (low power)
(Meigs, J. V. *Tumors of the Female Pelvis*, The Macmillan Company, 1934)



Fig. 22.—Photomicrograph of adenocarcinoma of the body of the uterus, medium grade (low power).
(Meigs, J. V.· *Tumors of the Female Pelvis*, The Macmillan Company, 1934.)

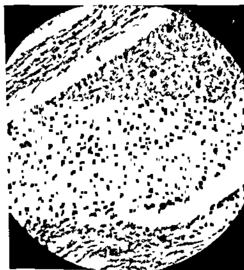


Fig 23 —Photomicrograph of carcinoma of the body of the uterus growing in solid masses, high malignancy (high power)
(Meigs, J V : *Tumors of the Female Pelvic Organs*, The Macmillan Company, 1934)



Fig 24 —Photomicrograph of epidermoid carcinoma of the body of the uterus, adenoacanthoma. Note the solid sheets of cancer and the epithelial pearls
(Meigs, J V . *Tumors of the Female Pelvic Organs*, The Macmillan Company, 1934)

which projects into the uterine cavity and demonstrates no tendency to invasion. If invasion of the wall occurs, it should *not* be called adenoma malignum. Novak thinks this would connote a higher degree of malignancy than the tumor presents, either clinically or pathologically.

Small regular low papillae of uniform character are encountered with cells showing occasional mitosis and a mild degree of hyperchromatism. The stroma is less abundant and there may be little connective tissue between the glands, which become pressed together. Large gland spaces may be found, containing



FIG 25 —Carcinoma at top of the fundus Note the extent of vaginal cuff and parametria removed

a few large cells with an occasional mitosis. The gland pattern is not nearly as atypical as one finds in the higher grades of malignancy. The degree of differentiation is slight, perhaps not exceeding 25 per cent

Grade II or Adenoma Malignum The picture is an accentuation of that described above, in that there are enlarged masses of glands which are both dilated and elongated The entire tumor is full of these giant glands with multiple papillary convolutions which encroach on the stroma to the point where it is practically nonexistent and the adjacent glands seem to be in direct contact *Abundant mitosis with hyperchromatic nuclei appears among the* cuboidal and cylindrical cells which are so packed one on the other that they appear to be in layers which tend to push in and occlude the lumen of the gland. The glands are so numerous and the supporting stroma is so scanty that it is small wonder that some evidence of necrosis may appear. It is perhaps this tendency to break down that explains the shorter duration of symptoms in this group Early bleeding, earlier attention, and better prognosis may be anticipated The degree of differentiation runs between 25 and 50 per cent according to Novak. The polarity of tissue is everywhere maintained. Healy feels that wherever there is a tendency to form solid masses which invade the stroma, the tumor should be classified as adenocarcinoma.

Grade III. Some parts of this tumor may resemble the picture presented in grades I and II as noted in the tendency to maintain the gland pattern, but the entire appearance is more atypical. There is a definite loss in polarity with the tumor growing in solid masses of cords and columns throughout. These masses may extend into the musculature. At some portions there may appear to be a thwarted effort to reproduce the gland pattern. The cells themselves are more atypical though some of them may show evidence of maturity and even secretion during the reproductive period. The signs of anaplasia are more marked with a differentiation noted in a proportion of 50 to 75 per cent.

Grade IV. In this instance the loss of polarity is complete. Masses of atypical cells, both round and polyhedral, are found growing in sheets and cords and filling the lumen of what remains of the gland structure. For the most part



Fig 26 –Photomicrograph of specimen shown in Fig 25 Early carcinoma of the fundus, grade II

the glandular arrangement has disappeared, but careful examination of other areas may show persistence of the gland pattern. The nuclei are small and hyperchromatic, with scanty cytoplasm and abundant mitosis. The sheets of cells can be found invading the muscle. In this group metastases appear early and the entire pathologic picture may be reproduced in the regional nodes The loss in differentiation is nearly complete Because of the tendency to form solid masses without evidence of gland structure, the tumor may be confused with lymphosarcoma or more likely adeno-acanthoma.

Incidence in the Different Grades

By whatever classification, the percentage of patients seems to be about 60 per cent in the low or medium grades of malignancy, with about 40 per cent in the more undifferentiated tumors. Miller reviewed his material according

to both the Ewing-Mahle classification and the simpler all-inclusive method proposed by Meigs and Scheffey, with the following results:

Ewing-Mahle			*Miller, according to Scheffey*			*Scheffey's material*		
	Number	Per Cent		Number	Per Cent		Number	Per Cent
Grade I	23	14 7	Low	101	64 7	Low	22	32 8
Grade II	78	50	Inter	50	32	Medium	27	39 7
Grade III	50	32.	High	5	3 2	High	18	26 4
Grade IV	5	3 2						

Meigs and others have found a higher percentage among the medium grades of malignancy. Fricke for example found 56 per cent to be in Grades I and II, 31 per cent in Grades III and IV, and 13 per cent ungraded.

Prognosis

In general, it may be said that the prognosis varies with the grade, for the best results are reported in the lower grades of malignancy while the poorest results appear among the Grade IV cases Grade I lesions have a relatively shorter duration of symptoms which may explain in part the better results obtained in this group The age difference has some bearing on the end result, for Murphy noted a five year age difference between the lower grades of malignancy which proved to be operable and the more highly undifferentiated tumors classified as inoperable Likewise the patients with grade I and II lesions are more than likely to have a natural menopause, 86 per cent; while only 61 per cent of the higher grades of malignancy had the same experience.

Grade, however, is only one of the several factors bearing on prognosis. Enough difficulty is encountered in grading the tumor from sections of the entire uterus to expect that any indication of the proper treatment can be obtained from information gathered from frozen sections of the endometrium The grade of tumor should not therefore determine the type of treatment to be employed.

Histology of Adeno-acanthoma

Islands of proliferating squamous cells appear not infrequently in cases of adenocarcinoma. There appears to be a combination of glandular and epidermoid epithelium varying in quantity and extent of pearl formation. In most instances the glandular element predominates. Sheaths of flat keratinized malignant cells may occur in areas separate from the adenocarcinoma element or they may be intermingled When the metaplasia is extreme, broad solid fields of cells may be found pushing in between the gland lumen and may actually give the appearance of growing into the gland lumina displacing or at times obliterating the epithelium The cells may be entirely large or groups of small cells may make up the tumor, with or without pearl formation. Hyaline degeneration of the squamous cell masses may be present, and at times calcification of the pearls They may take origin from isolated foci or develop diffusely The masses frequently invade the muscle wall

Although the tumor for the most part is predominantly glandular, the squamous portion may assume the upper hand. The source of this squamous cell proliferation is highly speculative and its prognostic significance extremely controversial

Embryologic Source Meyer postulates that in the third or fourth month of

intra-uterine life squamous epithelium extends high into the cervical canal. At about the sixth month the cylindrical epithelium of the fundus grows down and replaces it. Basal cells may then be left beneath the glandular epithelium. Later, under stress, the cylindrical lining breaks down and the squamous lining begins to proliferate. Nathanson found squamous cells in the newborn and in infants up to two years, and Ewing has confirmed their presence.

It is also possible, inasmuch as the genital tract epithelium has a common origin from the müllerian duct, that some of the undifferentiated cells may be found in the uterine fundus. Inasmuch as they retain the power to differentiate as they will, they may in later life form a squamous type epithelium.



FIG. 27 —Endometrial hyperplasia with stilbestrol effect regarded as benign.

Metaplasia. Ewing advances the theory that adeno-acanthoma results as an actual metaplasia in the glands of the uterine body. This has been known to occur during menstruation and in pregnancy as well as in response to chronic infection as one sees in a pyometrium Broders, quoted by Schattenburg and Ziskind, does not believe that squamous epithelium derives from the well differentiated columnar cells but that the regenerative cell has the power to differentiate into either the secreting glandular type of cell or the protective squamous cell type. Experimental evidence by Murray is cited in proof. A variety of names has been given this observed phenomenon, such as squamous metaplasia, epidermization, and leukoplakia.

Presence in Hyperplasia. It is also found in other benign conditions such as hyperplasia of the endometrium. It is thus possible that such transformations may be secondary to estrogen stimulation Taylor quotes animal experiments to suggest that in animals at least the appearance of stratified squamous epithelium in portions of the endometrium is commonly considered as an estrogenic manifestation.

It is thus obvious that squamous metaplasia of either the surface or the glandular epithelium does take place in benign conditions as well as, and perhaps more

frequently than, in carcinoma of the endometrium, but that the source for the development of these cells is open to debate.

Significance. The actual significance of their presence is likewise controversial and depends in part on the pathologic interpretation.

Where areas of squamous cell proliferation are found in relation to benign hyperplasia, the resultant pathologic picture appears much more violent, according to Novak, than can be justified clinically. These areas are not malignant. While the cells may be atypical in size and shape and may contain large and dark-staining nuclei, there are none of the other evidences of nuclear activity



FIG 28 —Estrin-effect hyperplasia Adenocarcinoma *in situ*

to suggest the presence of carcinoma Novak believes that the diagnosis of adeno-acanthoma is not infrequently made in cases of benign hyperplasia associated with these squamous islands Novak speaks of 24 cases of this sort where curettage was performed and no subsequent carcinoma developed.

If the diagnosis is to be based on the predominance of the gland elements over the squamous elements, then the incidence of adeno-acanthoma will be low Novak believes that the evaluation of the malignancy depends on the behavior of the glandular elements rather than the squamous portion Murphy found but 2 in 197 fundal carcinoma, Lindsay 3 cases in 70, Healy and Cutler 3 cases in 100, and in 1936 Gellhorn could find only 25 cases reported in the literature. Miller on the other hand found that 15 per cent of his series was adeno-acanthoma If any part of the squamous portion of the tumor appears malignant it has been our habit at the Massachusetts General Hospital and the Pondville State Cancer Hospital to regard the tumor as an adeno-acanthoma We thus find that our incidence in both institutions is 22 per cent.

Importance It is also our belief that the tumor behaves differently in the fundus of the uterus The survival figures following surgery for this lesion are comparable to those obtained in adenocarcinoma, but we agree with Ferguson

that the tumor is resistant to radiation. Our experience likewise confirms the observations of Schattenburg and Ziskind who in an extensive study found that adeno-acanthoma behaved differently in that metastases were more frequent and more extensive than in adenocarcinoma of the fundus. More extensive surgery with bilateral pelvic lymphadenectomy is indicated for this type of pathology.

TREATMENT

While the accepted form of therapy for cancer of the endometrium may be primarily surgical or radiation or a combination of both, it is impossible to standardize the treatment to the point where one can say that all patients should be treated by one method to the exclusion of the other. There has been a recent tendency to regard cancer of the endometrium as a single clinical and pathologic entity much as we have done for cancer of the cervix.

Standardization

There is such a wide variety of factors bearing on the choice of proper treatment for the individual case of carcinoma of the endometrium that no attempt should be made to standardize therapy. In addition to the pathology of the primary tumor, the associated local pathology, the coexistent systemic disease, and the age and size of the patient all have a direct bearing on the choice of the method for treatment. The surgeon must decide whether the case is suitable for a primary surgical procedure or whether radiation alone should be the sole treatment. If surgery alone is to be used, should operation be followed by external radiation? If radiation alone is to be employed, how and in what dosage is it to be given? Should local intercavitary radiation be followed by roentgen therapy? If preoperative radiation is to be used in conjunction with surgery, should it be given in the form of radium or as external radiation and in what dosage? These are but a few of the problems inherent in therapy for carcinoma of the endometrium It should be our aim to offer the individual patient the best we have for her particular problem in the light of our experience with the different types of treatment.

Experiments in Technic

Our experience is constantly being broadened and our previous conceptions revised as we become more familiar with the armamentarium provided for treatment The literature abounds in experimentation with ways and means of applying local radiation to the unseen tumor within the uterine cavity. The proper dosage and timing are in no sense standardized. The same may be said for external radiation where machines of varying voltage are asked to deliver uniform cancerocidal doses of radiation to a tumor which cannot be visualized and whose ramifications are uncertain. Various methods are suggested and portals of entry employed to accomplish this end. Such experimentation is commendable and the end results may be expected to reflect the effort to improve the technic of radiation. Heyman has declared that any improvement in the prognosis of carcinoma of the endometrium is synonymous with improvement

in radiation therapy. To his mind the surgical technic for intra-uterine cancer has been brought to such perfection that further development is hardly to be expected. With this point of view we are definitely not sympathetic, for with a more enlightened concept of the natural spread of the disease, supplemented by the recent adjuncts to surgical treatment, such as blood and fluid replacement and the antibiotics, the possibilities of a more vigorous surgical approach to the problem are now being explored.

The choice of therapy is not concerned with whether surgery is better than radiation, but rather which mode of treatment is most likely to produce a favorable result for the individual patient. It is well to keep this point firmly in mind while evaluating the various methods of therapy.

Optimum Type of Treatment

There is general acceptance among modern writers that the ideal type of treatment calls for preoperative radiation followed by total hysterectomy with bilateral salpingoophorectomy some six to eight weeks later. The radiation may be either intercavitary radium or external radiation. Certain surgeons, although they are in the minority, prefer to remove the uterus through the vagina The routine postoperative external radiation treatment following surgery has some advocates, while a few radiate the vaginal vault after operation with radium plaques

Radium and Surgery It is reasonable that surgery should be the main buttress upon which therapy is erected. Because the disease is notoriously slow in its rate of growth and metastasizes only late in the disease, it would seem logical to remove the entire uterus inasmuch as the tumor is encapsulated within thick muscle walls of the uterus itself.

Preoperative Radiation Preoperative radiation as an adjunct to total removal of the uterus and adnexa would appear to be a completely logical procedure. Inasmuch as there appears to be a definite relationship between the rate of cure and the size of the uterus, improvement in results may be expected if the extent of the primary tumor can be reduced by radiation as a preliminary to surgery. In addition to the reduction of the element of infection, the tumor cells may be either destroyed or rendered less viable This would automatically reduce the hazards of operation by cutting down the postoperative infection as well as the chance of displacing active tumor cells on the fresh operative sites of the abdominal or vaginal incisions, thereby minimizing the risk of recurrence in these areas There is likewise the possibility that the effect of radiation may extend to the lymphatics of the adjacent parametrial and paravaginal tissues. Because such results can be obtained without increasing the technical difficulties of the operation, radiation as a preoperative procedure has been popular. Certainly neither the mortality nor the morbidity has been appreciable from surgery following radiation It has been common practice to delay six to eight weeks after radiation before doing the hysterectomy, to permit the inflammatory reaction, incident to the use of radium, to quiet down and permit the tissues to recover. This delay has been considered as a disadvantage of this form of treatment. If the tumor cells have been inactivated during this time, as Schmitz and others believe, the disadvantages are more apparent than real.

RADIUM ALONE

Not all authors concur in the belief that surgery is the basic method of attack on this form of malignancy. Heyman, for example, who has had a wide experience with radiation and presents figures of end results that are hard to approach, much less equal, has always been a staunch advocate of intracavitary radium as the treatment of choice, reserving surgery for the treatment failures from radiation. Kaplan likewise believes that the criticism of radiation as a form of therapy is less a criticism of radiation than of our methods of applying radium. With improvement in technics may come improvement in results. This is the basis for Heyman's contention.

The two schools of therapy then are represented by those who believe that intra-uterine radium properly given is adequate for cure of the disease and a larger group which recognizes the advantages of radium or irradiation but remains convinced that surgery with total removal of the uterus and adnexa should follow a preliminary radiation if the best results are to be obtained.

Factors Modifying Treatment. Unfortunately as Brindley has observed, the pathology, extent of disease, and general condition of the patient are bound to modify the choice of treatment. For example, certain types of intra-uterine pathology, notably adeno-acanthoma, are notoriously resistant to radiation. It would seem illogical in this group to employ preoperative radiation. Healy feels the same way about the lower grades of malignancy such as adenoma malignum grades I and II As far as adeno-acanthoma is concerned, it is unfortunate that pathologic confirmation of its presence is extremely difficult on the basis of the examination of the curettings by frozen sections. It is thus obvious that many cases of adeno-acanthoma have received preoperative radiation. Except for the delay incident to its use, no major damage has resulted, for the survival figures for adeno-acanthoma treated by radium and surgery parallel those for adeno-carcinoma treated in the same manner. The only advantage might come from the reduced risk of infection Where the diagnosis can be determined at curettage, immediate surgical intervention should follow, thereby reducing the risk of the double anesthesia in this older age group and lessening the financial burden of double hospitalization.

Conversely, not all patients with carcinoma of the endometrium are good operable risks independent of the extent of disease within the uterus. Heyman finds that of the 85 cases a year referred to the Radiumhemmet over 50 *per cent* are not suitable for surgery when first seen From 10 to 15 per cent of the total are inoperable because of the extent of the disease, though this figure shows some improvement in recent years. About 40 per cent of the total are inoperable because of age, obesity, or associated systemic disease Other more surgically minded writers place the operability rate at about 70 per cent, though McLennan found that only 53 per cent of his cases could receive the routine treatment of radium followed by surgery. Analyzing the reasons why *the standard* treatment was abandoned in favor of radiation, McLennan gives percentages for the extent of disease and age and obesity complicated by systemic disease which reverse those of Heyman.

It is thus obvious that it is extremely difficult to standardize treatment in this group of elderly women who have carcinoma of the endometrium The problem

is not made any less complex by the often repeated assertion that the operability in these patients cannot be determined on the basis of a routine pelvic examination.

ROENTGEN THERAPY

When contemplating the use of external radiation in the form of roentgen rays it is well to have clearly established the aim in giving such treatment. (1) Roentgen therapy may be given as a preoperative preparation for subsequent surgery, as employed by Miller. In this instance, roentgen therapy takes the place of intercavitary radiation. (2) Randall and Ward are both concerned about the loss in time incident to preliminary radiation and suggest a program of immediate surgery to be followed by external radiation (3) Kamperman, on the other hand, believes that intercavitary radiation supplemented by roentgen treatment gives a homogeneous radiation throughout the pelvis that cannot be achieved if the uterus has been removed (4) Where the disease has extended beyond the uterus, most authors agree that roentgen therapy may obliterate disease incident to lymphatic spread, whether employed as an adjunct to radium, as definitive treatment, or as a preparation for surgery. Miller goes so far as to suggest that external radiation may destroy disease that has extended to the tube or ovary.

Disadvantages. Miller agrees with Ward that in the presence of excessive obesity the basic radiation should be by intercavitary radiation due to the difficulty in securing uniform penetration which can be considered as cancerocidal Kamperman believes that the use of supervoltage x-ray of the 600 KV type will be sufficient even in these cases to secure an adequate depth dose of cancerocidal radiation without overly destructive action on the skin of the portals of entry or upon adjacent viscera The obesity of the patient remains as a definite objection to the use of external radiation.

Advantages. Where the patient is not too obese, external radiation, according to its chief exponents, Miller, Schmitz, and Kamperman, accomplishes much that can be achieved by radium without some of the disadvantages of the latter. The two main advantages appear to be that the ease of application, involving no manipulation of the uterus other than that necessary to make a diagnosis, tends to reduce the danger of manipulative spread at the time of operation. The chief advantage would appear to be the effect on the outlying cancer cell and the partial obliteration of the lymphatic chain Just what the effect on the primary tumor within the uterus may be is debatable. Miller believes that while the primary tumor may not be destroyed, the cells may be attenuated in viability. Schmitz in his studies on residual carcinoma found persistent disease where inadequate radium treatment was given, but none in the face of adequate roentgen therapy. He therefore concludes that roentgen therapy is useful not only for the adjacent parametrium and lymphatics but for its effect on the primary intrauterine tumor as well.

Preliminary Curettage We are in complete agreement with Healy and with Ward in condemning the practice of giving roentgen treatment as a preliminary to subsequent surgery without the benefit of a diagnostic curettage Since the vaginal smear technic is subject to 20 per cent error, the primary diagnostic measure is the curettage. To give roentgen treatment in the absence of a positive

diagnosis of endometrial carcinoma would be inexcusable. Inasmuch as it is essential that a primary diagnosis of carcinoma be obtained before instituting treatment, curettage under an anesthetic is a basic requirement. Ward, Healy, and Scheffey, among a vast array of surgeons, believe that it is logical to have radium available for application immediately on receiving pathologic confirmation of malignancy within the uterine cavity. *The basic form of effective therapy* is regarded as surgical and the time lost if roentgen treatment is given may be detrimental to the eventual prognosis.

As Supplementary Treatment. Where radiation treatment is to be definitive, roentgen irradiation may well be used as a supplement to intercavitary radiation. Inasmuch as 40 per cent of the patients receiving radiation as the sole form of treatment do so because of the spread of the disease beyond the uterus, such an adjunct must be of value. When the combination is employed it is well to have a well planned treatment designed to give proper balance to the two elements in order that effective uniform radiation may be given to the primary tumor as well as to the potential field of extension. Maximum dosage of both radium and roentgen ray may result in the overradiation with a marked increase in morbidity and mortality. It may be necessary to reduce the dosage of the intercavitary radiation if full tolerance doses of roentgen rays are to be administered. McLennan traced a primary mortality of 8 per cent directly to full doses of x-ray following complete intra-uterine radiation.

Vaginal Vault. Roentgen therapy has been employed as a prophylactic measure in conjunction with local radium to the vaginal vault in the postoperative period by both Smith and Fricke

There can be no doubt that roentgen treatment may be used either in place of radium or as a supplement to both surgery and radium in both the preoperative and postoperative period. It would appear again that the problem is not whether x-ray is better than radium but rather what is best for any one individual patient.

RADIUM THERAPY

General Consideration

Either by choice or because the patient is deemed unsuitable for operative interference through extent of disease, age, obesity, or concomitant systemic disease, radium may be elected as definitive treatment. In addition, radiation either in the form of radium introduced by an applicator into the uterine cavity or employed as external radiation through x-ray is commonly used as an adjunct to subsequent surgery. The problems posed in management are dissimilar only in dosage. Where the patient is regarded as operable, the surgeon may have to face the decision as to whether full radiation has any advantage over surgery or radiation plus surgery For the remaining group, radiation alone is possible, with the chief consideration being given to the question of whether the patient is a suitable candidate for complete radiation or modifications of the same Whether radium is employed with definitive treatment as an objective or is to be followed by surgery at a later date, the manner of application to the uterus and the problems associated with this procedure are of basic importance.

Application to the Uterine Cavity

Inasmuch as the dimensions of the uterine cavity are subject to great variation, adequate homogeneous radiation throughout the entire uterine canal is not easy to achieve. Where the presence of an eccentrically placed or submucous fibroid distorts the canal, the problems of adequate radiation are multiplied. Moreover, the major consideration is the application of a cancerocidal dose of radium to the tumor and its ramifications We are forced to radiate the entire uterine cavity, for we have only the curet or perhaps some help from hysterography to determine where the tumor is actually located Roentgenographic visualization of the uterine cavity or hysterography is accomplished by injecting radiopaque iodized oil into the uterine canal followed by roentgenograms. Such localization is not in general usage because of fear that trauma incident to its use may spread the disease LeClerc and Kaplan have had considerable experience with hysterography in outlining the tumor within the blind uterine cavity, but such experience has been limited. Neither the curet nor x-ray visualization gives any indication of the ramifications of the tumor beyond the point of origin within the uterus. Microscopic examination of the extirpated uterus with its parametrium and adnexa alone gives any idea of how far the tumor has extended.

It is not surprising then that radium treatment of the uterine cavity for carcinoma of the endometrium is far from ideal. It is easy enough to miss a small carcinoma of the endometrium situated at the cornua with a diagnostic curet. To deliver a cancerocidal dose at such a tumor site can therefore become a formidable problem To radiate adequately a large irregular cavity distorted by the presence of fibroids, submucosal or otherwise, is a feat in itself. Where a small carcinoma lurks at the top of the fundus or behind a submucous fibroid, proper application of radium in sufficient dosage to eradicate the tumor permanently is indeed difficult Radiation in a large irregular uterine cavity is bound to be unreliable Where an unknown extent of tumor is present in an invisible field of uncertain dimension and contour, it is obvious that the surgeon must fall back on his only recourse—that of trying to provide a uniform cancerocidal dose of radiation to the entire uterine cavity As a result some parts of the endometrium are left untreated while other areas are overtreated, with resultant necrosis There is some evidence to show that such overly intensive radiation may destroy natural tissue resistance to the point where not only the effect of radium is nullified but the spread of the disease is accentuated At any rate it is small wonder that recurrence following intra-uterine radiation is common Even Heyman agrees that the most successful cases for intercavitary radiation appear among the group where the carcinoma arises in a narrow uterine cavity.

Residual Carcinoma Following Intra-uterine Radium

The best evidence that intercavitary radiation is unreliable is attested to by the many studies available in the literature indicating the relatively high percentage of patients showing residual carcinoma among the uteri extirpated following radiation.

This may in small part be due to the type of histology of the tumor presented for treatment. Healy suggests that not all carcinomas of the fundus have the same cellular structure. There are marked variations in degrees of malignancy and

radiation sensitivity. Our experience at the Pondville Cancer Hospital of the state of Massachusetts and at the Massachusetts General Hospital, for example, is in complete agreement with the statement of Ferguson that there is no reported case where adeno-acanthoma disappeared after radium treatment. Healy adds his assent to the above observations. Formerly adenoma malignum grades I and II were regarded as resistant to radiation. This observation may be faulty, for Fricke produced 39 per cent of five year cures in these grades of tumor. These figures parallel the anticipated over-all cure rate for radiation treatment of all grades of malignancy of the endometrium

Regardless of the histologic type, there appears to be adequate evidence that radiation at least as given preoperatively does not produce actual destruction and disappearance of the carcinoma in more than half the cases in which it is employed. The reports in the literature vary, from 12.5 per cent to 89 per cent of cases showing persistence of residual carcinoma following the use of intra-uterine radiation In part this difference may be due to the wide variation in dosage and type of applicator employed.

Diligence of Search. The more probable explanation, however, as Stowe, Warren, and Novak have pointed out, can be traced to the diligence of microscopic search. In most instances specimens from the removed uterus are taken from the obvious sites of radiation reaction or grossly involved areas. Serial sections are needed for an accurate appraisal. Donovan and Warren found for example that in some instances the carcinoma was undisturbed although the myometrium was badly damaged. Moreover Stowe discovered 19 instances among 53 cases intensively studied by multiple serial sections where carcinoma had been found deep in the muscle although none had appeared on the surface.

Size of Dose. The type of application and size of the dose may play a role, for Schmitz using dosages heavier than those employed by Warren, Stowe, and Novak could find no residual carcinoma in 4 or 5 uteri removed after radiation and subjected to serial sectioning Seven more cases were adequately radiated but no hysterectomy was done. Four of these later were subjected to curettage and no carcinoma was found. On the other hand, one died later of peritoneal metastases, indicating that the results of curettage cannot be advanced as evidence for or against invasion of the myometrium or extension to the lymphatics. Stowe employed a jointed applicator with the radium in tandem to give doses of at least 4500 mg. hours. Residual carcinoma was noted in 56.5 per cent of the cases, but where x-ray was added to the intercavitary radiation the percentage of patients with persistent disease dropped by 41.2 per cent. Healy and Brown find that the percentage of residual carcinoma dropped from 60 to 40 per cent when a larger dosage of radium is given It is thus possible that the size of the radium dose given may have a bearing on the amount of residual disease following treatment.

Question of Viability It is perfectly possible that the importance of residual carcinoma in uteri removed after radium therapy has been overemphasized. No one is completely sure that the cancer cells seen under the microscope are viable following radiation. The cells could be *inactive* or attenuated in their virulence. If the cells are momentarily encapsulated and rendered less lethal, then the mere presence of residual tumor, as seen microscopically, cannot be taken as a

measure of the effectiveness of radiation, at least as far as its use as a preoperative procedure is concerned. It is of utmost importance when we come to rely on intra-uterine radium as the sole means of treatment.

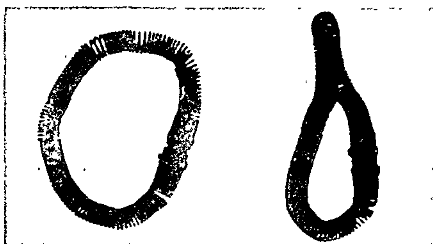


Fig 29.—Kaplan's radium ring
(Kaplan, I. I *Radiology*, 39 135, 1942)

Residual carcinoma is nevertheless a common finding, regardless of the dosage or the type of applicator, as suggested by the following statistics published in the literature. Whether the carcinoma is viable or not is debatable.

Sackett	33 per cent
Healy	40 per cent
Novak	50 per cent
Stowe	50.9 per cent
Scheffey	54 8 per cent
Brindley	55.8 per cent
Corscaden	61 9 per cent
Warren	89 0 per cent

Types of Intra-uterine Radium Application

In a real effort to overcome the difficulties inherent in delivering uniform cancerocidal radiation to a tumor that can neither be seen nor felt, within a blind cavity whose contour and dimensions are never constant, many authors have demonstrated real ingenuity in the type of applicators devised. Kaplan points out that the failures in radiation may be traced to faulty technic for, as Randall says, it is obviously not enough simply to insert radium in the uterine cavity.

The following methods of treatment and types of applicators have been employed as a means of cutting down the percentage of residual carcinoma and increasing the effectiveness of intra-uterine radiation

At the Pondville Hospital the uterus is measured with a hysterometer. A gold radon tube to suit these measurements is then incorporated into a Monel applicator and inserted in the uterine cavity. While this method does not take into consideration any measurement of the cavity other than depth, it has the advan-

tage of ease of application with little associated risk. This is an improvement on the single rubber catheter or metal applicator of silver or platinum in which the radium needles were placed in tandem. Most authors now believe that the single application is ineffective, for disease in the cornua is unlikely to be affected, and



Fig. 30.—Kaplan's radium ring.

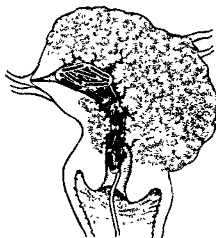


Fig. 31.—Diagrammatic representation of Kaplan's ring.

efficiency is limited to the tissue immediately adjacent to the applicator. Schmitz employs a Y-shaped tube in an attempt to conform to the established conception of the contour of a normal endometrial cavity. Stowe, after direct measurement of the uterine cavity, employs fine platinum capsules placed in series in a ligated rubber tubing in such a manner that when the tube is bent between the second and third tandem the uterus will be radiated by two capsules on each side with one at the base. The concentration of radium will be at the fundus and body of the uterus. Crossen, Friedman, Martin, Arneson and Pfahler all employ the

principle of multiple small radium applicators held in place by wires or hinged tubes Kaplan regards all of these methods as complicated and cumbersome and suggests the following procedure:

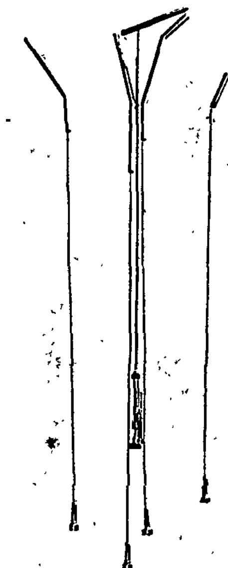


FIG 32 —Friedman's hysterostat
(Kaplan, I. I · *Radiology*, 39 135, 1942)

The contour of the uterus and the location of the carcinoma are determined by radiographic study with visco-rayopake. A malleable radium ring is then constructed which is flexible enough to adapt itself to the contour of the cavity in direct relation to the tumor This application is further supplemented by a rubber tandem containing radium, as well as a colpostat to the vagina. The fact that incision of the internal os is recommended to permit ease of insertion and egress does not speak for facility in application. Without question Heyman has had

by far the greatest experience with the method of introducing multiple foci of radiation into the uterine cavity in order to secure uniform radiation. Multiple

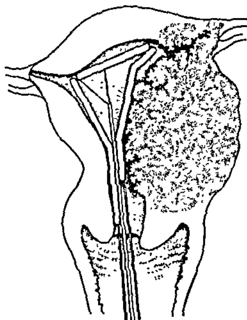


FIG. 33.—Diagrammatic representation of Freidman's hysterostat (Ackerman, L. V., and del Regato, J. A.: *Cancer, Diagnosis, Treatment, and Prognosis*, C. V. Mosby Company, 1947.)

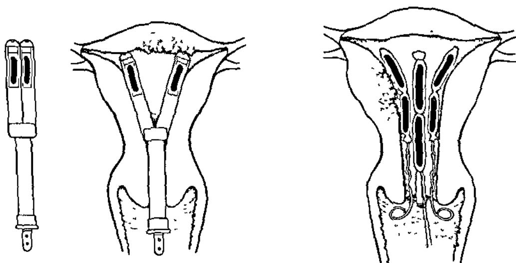


FIG. 34.—Schmitz type of applicator (Ackerman, L. V., and del Regato, J. A.: *Cancer, Diagnosis, Treatment, and Prognosis*, C. V. Mosby, 1947.)

FIG. 35.—Crossen type of applicator (Ackerman, L. V., and del Regato, J. A.: *Cancer, Diagnosis, Treatment, and Prognosis*, C. V. Mosby, 1947.)

small cylinders of uniform size and shape and of equal radium content are packed into the uterine cavity until filling is complete. The cylinders are held in position by a specially constructed tube holder. Perforation of the uterus in applying the cylinders is not unknown and removal is not without its problems.

In addition to the disadvantage mentioned above, Heyman mentions placing a glass drain in the cervix to prevent stenosis.

Sampson, experimenting with Heyman's idea, filled excised uteri with sodium iodide to make the cavity opaque to x-ray. An attempt was then made to dis-



Fig. 36 —Martin type of applicator. (Kaplan, I I *Radiology*, 39 135, 1942)

tribute the capsules evenly over the surface of the uterine cavity. Roentgenograms taken to show the distribution of the capsules indicated that, under the most favorable conditions and in the absence of complicating pathology such as polypi or submucous fibroids, the chances of getting uniform filling were no better than even. It is possible that Morton and Hahn may acquire a more uniform radiation than has so far been acquired by their experimental use of an

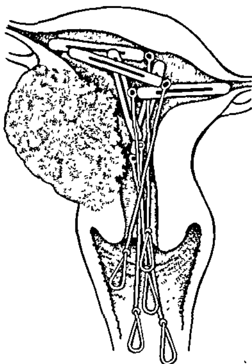


FIG. 37.—Diagrammatic representation of Martin applicator.
(Ackerman, L. V, and del Regato, J. A. *Cancer; Diagnosis, Treatment, and Prognosis,* C. V. Mosby Company, 1947.)

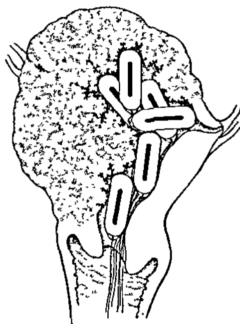


FIG 38 —Heyman's multiple capsule method.
(Ackerman, L. V., and del Regato, J. A: *Cancer, Diagnosis, Treatment, and Prognosis,* C. V. Mosby Company, 1947.)

intra-uterine bag distended with radioactive isotopes in a fluid media. The idea is worthy of speculation.

Bowing and Fricke attempted to accomplish uniform radiation to the uterine cavity by other methods than employing multiple mechanical radiation foci. The

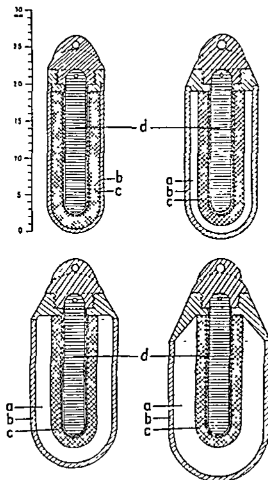


Fig 39 —Detailed description of individual capsule. (Kaplan, I. I *Radiology*, 39:135, 1942)

basic principles employed by them is that of the broken dose technic. Single straight brass applicators filled with gamma ray radon of 50 mc. each are used The patient is placed in the knee-chest position and with the minimum of trauma, because of the friable uterine walls, two brass tubes are inserted into the depths of the cavity and left in place for 24 hours The procedure is repeated in three or four days to the mid-portion of the body of the uterus and again to the cervix. Thus by repeated insertions it is hoped that uniform radiation as well as individualization in treatment may be obtained. There appears to be some overconcentration in the mid-portion of the average size uterus through overlapping. Fricke suggests that while both ends receive between 5,000 and 8,000 r the center may receive as much as 24,000 r. The intra-uterine radiation is supported by vaginal application depending on the evaluation of need.

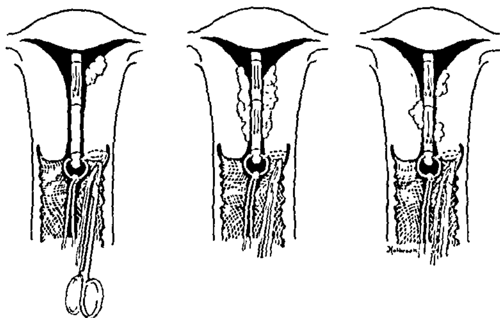


FIG. 40.—Single platinum type of applicator, demonstrating method of retaining applicator within the cavity.



FIG. 41. [illegible] cavity.

It is thus obvious that the problem of radiation of an unseen tumor, of varying malignant potential, existing in a cavity whose dimensions and contour are uncertain, has not yet met with satisfactory solution despite earnest experimentation. All authors are in agreement that despite the many disadvantages of radium

treatment good results are obtained both as definitive treatment and as a supplement to surgical intervention.

TECHNIC OF RADIUM APPLICATION

On the basis of the history and physical examination plus the information gathered from the vaginal smear the suspicion of carcinoma of the endometrium is aroused. The final decision rests on the microscopic examinations removed at the time of curettage. The curettage is therefore carried out with radium available.

Anesthesia. On the receipt of a positive report, the radium is immediately applied with the patient under an anesthetic which by choice should be either low spinal or gas, oxygen, ether, or any complete general anesthesia that permits complete relaxation. The outline of the uterus is difficult enough to determine in obese women without complicating the evaluation by having the abdominal wall incompletely relaxed, under pentothal anesthesia for example. The prognosis, choice for or against surgery, or the use of x-ray as a supplement, will depend on the estimate of extent of the disease as measured by the fixation and size of the uterus, as well as on the evaluation of the degree of infiltration of the parametria. The presence of associated pathology such as fibroid, pelvic inflammation, or adnexal tumors as well as vaginal extension of the primary intrauterine cancer may well influence the plan of treatment of the carcinoma of the endometrium Because of the handicap of not being able to see or feel the primary tumor, it is important to acquire as much information as possible in the obese patient in order to obtain some idea of the location of the tumor, and, if in any way possible, its extent. These data cannot be collected without satisfactory anesthesia.

Choice of Treatment. At this time the outline of treatment must be established. If, for example, the patient is obese, elderly, or is in poor general condition because of hypertension, diabetes, cardiovascular disease, or other systemic pathology, the choice will undoubtedly be for intercavitary radiation as the definitive form of treatment If in addition the disease has extended beyond the confines of the uterus or the uterus is enlarged by concomitant fibroids, the decision to employ roentgen treatment as a supplement later may be considered Whether it is given or not will depend on the response to the primary radium treatment. Where it is planned to use x-ray as a part of the treatment the dosage to be delivered as in the case of intra-uterine radium must be determined at the time of curettage.

On the other hand, an obese woman with disease beyond the uterus may be given intra-uterine radiation or roentgen treatment as a preliminary to surgery, provided she is in good general condition. The dose of intra-uterine radium will thus be different from that given for definitive treatment If the disease appears to have extended beyond the uterus or the uterus is overlarge, roentgen treatment may be used as a preliminary rather than radium, in the hope that the operative technical details be made easier and the risk of dissemination minimized

Scheffey, Ward, and Martin have popularized the procedure of having radium available at the time of the curettage with the amount of the dosage to be used dependent on rapid six-hour examination of the pathologic material removed at curettage. Depending on the factors outlined above, the radium is left in the

uterus a longer or shorter time to give dosage in keeping with the decision to employ radium as a treatment or as an adjunct to surgery at a later date.

Radium as Definitive Treatment

While Heyman considers surgery only where radiation fails, the majority of the world clinics employ radium for cure in two classes of patient: (1) in those in whom the disease is too extensive for surgery but where there is hope of at least palliation from radiation, (2) in the patient who is too poor a risk for surgery. In this group the radiation is designed to cure without incurring the risk of surgery. Approximately 30 per cent of any large series will be subjected to radiation The average age of the group subjected to radiation will be five to 10 years older than those subjected to surgery.

Technic and Dosage. The majority of surgeons apply a single application of radium in whatever type of applicator is available to them. The aim, even in the straight metal applicator or rubber tubing, is to obtain an even distribution of radium throughout the canal The dosage given varies widely in different clinics. Most authors now agree that doses approximating 6,000 to 8,000 mg. hours are needed where radium alone is to be used. In general, but depending on the amount of radium available in the clinic, 150 mg of radium, usually in the form of two or three 50 mg. tubes, are inserted in the canal to be left for a total of from 40 to 80 hours, depending on whether 6,000 or 8,000 hours are chosen or 150 mg. radium are used. This in turn depends on how much tumor is estimated to be present and how big the uterine cavity is felt to be at the time of curettage There may appear to be, for example, a small tumor in a large uterus or a large tumor in a small uterus and all grades in between.

The radium must remain within the uterus for an appreciable period of time. It is, therefore, important to insure its remaining in the same position as at the time of curettage. The individual specialized type of applicators has its own devices for retaining the appliances within the uterus Where a single applicator T rubber or straight rubber tube is used, a single mattress suture placed through the cervix and clamped without tying serves very well. The clamp is left in the vagina on the untied suture Removal of the clamp permits easy withdrawal of the radium It is absolutely essential that the radium be retained within the uterine canal If the radium should be inadvertently displaced and retract out of the canal, severe radiation necrosis of the vagina, bladder, or rectum might result To protect the bladder further an inlying catheter of the Foley type is inserted in the bladder and attached to closed or dependent drainage. In this manner the bladder remains deflated and the overdistended wall kept from contact with the point source of radium within the uterine canal

Divided Dose Treatment. The radium treatment may be repeated rather than applied at one time. Ward, for example, gives 2,400 to 4,000 mg. hours by two 50 mg radium capsules screened with 1 mm. of platinum and applied in tandem. If the case is regarded as inoperable, the application is repeated in four weeks' time. The amount of the dosage depends on the size of the uterus and the result obtained. This dosage is supplemented by roentgen ray. Schmitz, with his Y-shaped tube, repeats the initial 2,000 mg hours on the eighth and 16th day for a total of 6,000 mg. hours Roentgen treatment is given on the days when

no radium is employed. Heyman, using the multiple capsule technic to pack the uterus, gives two treatments of approximately 1,500 mg. each about four weeks apart. Fricke and Bowing are the foremost exponents of the divided dose method. After the diagnosis is established, the patient is placed in the knee-chest position and without anesthesia a single straight brass applicator containing two 50 mg tubes in tandem are inserted into the top of the fundus of the uterus. This is left for 24 hours or 2,400 mg hours Three or four days later the process is repeated in similar dosage to the "anterior portion of the uterine canal." The number of applicators and hence the dosage depend on the depth of the canal and the size of the uterus In addition the cervical portions of the tumor are radiated to prevent apical vaginal recurrence. Two or three treatments of 700 mg hours each are given at two to three weekly intervals. In addition, high voltage roentgen therapy is used as a supplement. It is interesting that Fricke divides the patients into four different groups depending on what he hopes to achieve for the patient in relation to the state of her general health and stage of the disease. (1) complete treatment, (2) limited, (3) prophylactic, and (4) abandoned Only 60 per cent of the entire radiated group complete the full treatment About 10 per cent less salvage is found in the group where only limited treatment can be given. This method permits the maximum degree of individualization.

Roentgen Therapy as Supplement. Whether roentgen therapy is a helpful adjunct in the cases basically radiated is difficult to determine. Fricke subjected about one-third of the radiated cases to x-ray but obtained the same percentage of cures as he had without external radiation. This probably can be regarded as evidence of increased salvage, for the patients receiving the additional radiation undoubtedly did so because of more extensive disease. Schmitz, Fricke, Scheffey, and Smith all employ external radiation following intracavitary radium. The dosage is delivered usually from a 200 KV machine through two to four portals depending on the size of the patient with a total dosage measured in air from 4,000-7,000 r

The general impression appears to be favorable to the use of x-ray as an *adjunct to intra-uterine radiation Most of the reported cases have been treated* with lower voltage machines than are now available The ability to obtain a more uniform depth dose with less dissipation on the skin and less dosage to the adjacent viscera is possible through the 600 KV machines employed by Kamperman, 800 KV, as used by Schmitz, and 1,200 KV of the Massachusetts General Hospital Improved results may be anticipated. There remain the disadvantages of the obesity of the patient and the possibility of visceral damage as one attempts to deliver cancerocidal doses deep in the pelvis Randall sounds a note of caution as regards overenthusiasm in the use of x-ray treatment for cure Because some hopeless cases have responded surprisingly well to the combination of x-ray and radium is not sufficient reason for employing the combination where there is a better chance of cure from radium and surgery.

PREOPERATIVE RADIUM

The Purpose. The study of Elton on 50 uteri removed following radiation confirms the clinical impression that no idea of the extent o

obtained short of hysterectomy. For that reason it is important whenever possible to follow intercavitary radiation or external radiation by hysterectomy. The purpose of preoperative radium is simply to sterilize the more sensitive elements of the tumor and minimize as far as possible the dissemination of the disease at the time of surgery. There may be some partial blockage of the regional lymphatics or effect on the cancer cells in the adjacent parametria. The number of parametrial and vaginal recurrences may thus be lessened. The majority of clinics now employ intra-uterine radium as a preoperative measure. This is true regardless of the fact that over 50 per cent of the uteri removed after six to eight weeks show residual carcinoma. The nests of cells present within the uterus after radiation may later become reactivated and cause death, but during the time the surgery is performed the cells may be encapsulated, nonviable, or attenuated in virulence. The operative hazard is definitely reduced. The combination treatment of intercavitary radiation followed in six to eight weeks by total hysterectomy and bilateral salpingoophorectomy may be regarded as the accepted pattern for treatment for carcinoma of the endometrium.

Dosage of Preoperative Radium. Inasmuch as the aim of radiation is not to secure permanent tumor death the actual dosage of radium may be less than that required for definitive radium treatment. Enough radiation however must be given to sterilize the cancer and, if possible, to reduce the bulk of the tumor as well as the size of the uterus In order to accomplish this at least 3,600 mg. hours of radium should be given with most authors employing about 4,500 mg. hours

The dangers of overradiating a small uterus have been noted by Scheffey. Following this amount of intracavitary radiation, no technical hurdles are anticipated at the time of surgery nor is morbidity increased While the dosage is pretty well standardized, the manner of application varies widely, with all manner of gadgets designed to overcome the difficulties of radiating an unseen tumor in a tortuous cavity The simpler methods are probably adequate where surgery is to be employed later, and certainly the risk of application is less.

Preoperative Radiation by Roentgen Ray

Miller is the chief sponsor of the preoperative use of x-ray to take the place of radium. He believes that there is a direct effect on the primary tumor cell and that carcinoma of the endometrium within the uterus itself is affected regardless of the type of pathology presented. Moreover, since the technical difficulties of providing uniform radiation to an irregular uterine cavity may result in certain areas being completely unaffected when radium is used, there is a real place for x-ray treatment inasmuch as the distribution of radiation is more uniform.

RADIATION PATHOLOGY

Homogeneous Radiation

The difficulties of homogeneous radiation of the uterine cavity with the type of applicators now in vogue has been stressed. It has been noted that certain parts of the endometrial cavity have been left untouched by radiation while other areas receiving the brunt of the radiation effect appear to have more than

enough. By his technic of employing a jointed rubber tube which when properly bent will provide a crossbar of radiation at the fundus with two lateral tubes on either side, Stowe theoretically achieves radiation of the entire cavity with gradations from the fundus to the cervix. If for example 50 mg. of radium are to be used the distribution in the ligated rubber tubing would be as follows:

7 mg.	When bent between the second and
10 mg.	third tandem the distribution of
15 mg	radium would provide a 15 mg. cross-
10 mg.	bar at the top with 17 and 18 mg. on
8 mg.	either side.

The dissemination of radiation would thus be balanced at both sides and the top but less radiation would be given at the internal os. The radiation effect of the uteri where no residual carcinoma was found was subjected to intensive scrutiny using multiple serial sections through the radiated areas

Pathologic Observations

Stowe found that there were three different radiation patterns: (1) A complete necrosis of the endometrium had taken place A pink mass could be seen extending for several millimeters into the muscle. No cell boundaries could be made out The demarcation was so irregular that it would appear to be produced by an infarct Small round cells together with polymorphonuclear leukocytes were observed between the area of necrosis and the normal muscle. (2) The majority revealed the endometrium completely replaced by a covering of granulation tissue, which while dense on the surface became loose as it approached the muscle which was completely untouched by the radiation. (3) The remaining group likewise showed a zone of granulation tissue to be present in which irregular gland spaces were found The distorted cells are often eosinophilic and vaculated containing pyknotic nuclei and granular cytoplasm For this reason they have been considered as possible damaged cancer cells though Stowe regards this as unlikely

Radiation Plaque

Sheehan has made a very thorough study of the effects of radiation upon the uterine endometrium associated with carcinoma A constant plaque-like area of coagulation necrosis usually appears at the internal os with zones of hyalinization and edema of the myometrium together with some endometrial hypertrophy. Grossly the plaque, which tends to extend up into the cavity rather than down into the cervix, is an irregular mass of partly soft and partly firm material elevated above the surface for about 6 mm and for the most part well demarcated The plaque likewise extends into the muscle for about 5 mm. It is interesting that all of the uteri were definitely larger than normal. The actual muscle bundles and even the individual muscle fibers were larger than normal. No diffuse muscular atrophy had taken place nor was there any evidence of widespread hyalinization, with subsequent contraction, despite full doses of radium as generally described The only changes noted were in the plaque and the immediately adjacent myometrium In the myometrium two definite zones appeared, the

superficial zone revealing hyalinization and edema with infection secondary to necrosis and a deeper zone demonstrating atrophic changes. In the zone of necrosis, only the muscular remains of the muscle cells can be seen, while pyknotic nuclei in small empty spaces separated from each other by thin bands of hyaline material are noted in the hyalinization zone. The endometrium is always destroyed. The latter zone is sharply demarcated from the area of necrosis Though hemorrhage and infection are present, Sheehan questions whether this plaque-like area is secondary to an infarct. The myometrium shows a direct effect of radiation rather than a reaction to the overlying area of necrotic



Fig 42—Radiation reaction. This demonstrates zones of radiation reaction from single tandem.

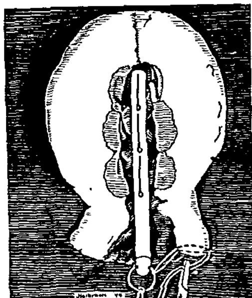


Fig 43—Drawing illustrating position of needles in a single platinum applicator in relation to the areas of reaction

tissue. The real danger in radiation, even when given in such quantities, is in all probability the risk of infection because of the thick muscle walls of the uterus Sheehan believes that it is highly possible that the location of this plaque at the level of the internal os is due to the fact that the applicator lies closer to the muscle wall at this point and is therefore recipient of the most intense radiation

Danger of Over-radiation

Necrosis of the tumor at this point may result according to Arneson in unrestrained growth of cancer rather than in eradication or control of the disease. The same observations have been made for cancer of the cervix. Normal tissue resistance is altered by the extreme degree of necrosis supplemented by infection There is some evidence to show from repeated biopsy studies and vaginal smears taken during radiation treatment that the response in the normal cell will indicate whether the tumor is radiation-resistant. The same factors may be at work in the body of the uterus as in the cervix. If this be true then some consideration must be given to maximal and minimal doses as well as more uniform radiation distribution

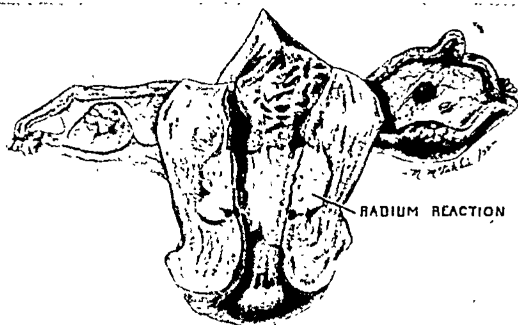


FIG. 44 —Drawing of actual uterus, demonstrating the intensity of local reaction at the internal os. This shows the intensity of the reaction at the internal os and the ease with which the top of the cavity may escape radiation.
(Meigs, J. V : *Tumors of the Female Pelvic Organs*, The Macmillan Company, 1934)



FIG. 45 —Extensive radiation necrosis.

Arneson has pointed out that the drop in intensity, within a few millimeters of the point source of radiation, is extreme It is thus theoretically possible that carcinoma located but a short distance away from any given radium tube or capsule may receive a sublethal dose which is completely inadequate. To step

up the dose is to run the risk of greater concentration at one point with increasing necrosis which may defeat the purpose without carrying enough intensity to all parts of the uterine cavity, and most particularly the tumor which may be situated anywhere in it. It would be more logical, therefore, to increase the number of radiation sources of lowered concentration and thus run less danger of overradiation. The method, employed by Heyman and also Arneson, is based on this principle which is fundamentally sound. Inherent in this method, however, is the danger of perforation of the uterus as the capsules are inserted.



Fig 46—Photomicrograph showing extensive radiation reaction

Time Interval before Surgery

The time interval following radiation before the definitive surgery is performed will of necessity influence the pathologic observations as to the persistence of carcinoma as well as the actual pathologic picture of radiation From the point of view of the residual carcinoma it would perhaps be more logical to perform the hysterectomy earlier than the arbitrary six to eight week interval commonly prescribed. There is some evidence that recovery of the tumor and reactivation of the growth may take place if the tumor is not completely destroyed On the other hand study of the post-radiated uterus, even at the end of six to eight weeks, may not give an accurate picture of the pathology of radiation. As Ackerman reminds us, most tumors, however radiation-sensitive, have a more or less prolonged period before final disintegration of the tumor can be anticipated.

From the point of view of radiation necrosis and persistence of carcinoma, it is obvious that the ideal homogeneous radiation of the entire uterus has not as yet been reached. Inasmuch as we have no idea of the location of the tumor within the uterus and remain uncertain about the extent of the ramifications of the disease within the wall, it will continue to be essential that the entire uterine cavity receive a uniform cancerocidal tumor dose. As regards the optimum time

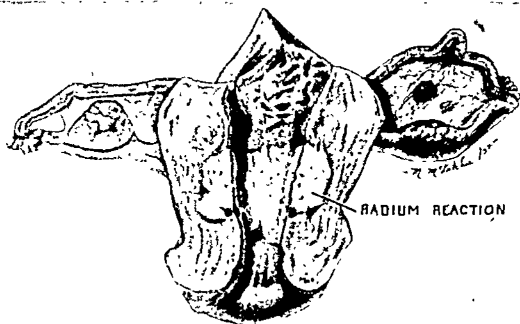


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Proctitis with severe diarrhea, nausea, and vomiting as well as pain are not infrequently seen during the course of treatment. Stenosis of the rectosigmoid or later fistula formation may appear after several years in a patient who has had evidence through severe proctitis or damage to the rectal mucosa in the course of treatment.

The complications of genito-urinary origin, particularly the bladder, are likewise common. Cystitis, owing to the proximity of the bladder to the radiation source, may be anticipated despite efforts to prevent it by the use of an inlying catheter and packing back of the bladder during the radium application. Ureteral stricture and hydronephrosis infrequently appear and are not nearly as common as noted during the treatment for cancer of the cervix.

Mortality. In general it may be stated that in the elderly obese poor risk group where radiation alone is the definitive treatment, the mortality from the use of radium is practically negligible. Masson believes that the mortality from radium should not exceed 2 per cent Fricke and Bowing in their series of 109 cases placed the figure at 2.6 per cent. Most of this mortality came in the advanced stages of the disease. The actual mortality from the use of radium alone approaches zero in most clinics.

When x-ray is employed as a supplement to radium the mortality increases and is probably attributable to the external radiation. Smith observed one death among 36 cases so treated. McLennan places the figure as high as 8 per cent. This is not surprising, for a dose of external radiation heavy enough to be cancerocidal deep in the pelvis of obese women could be expected to produce visceral damage.

TIME INTERVAL BEFORE SUBSEQUENT SURGERY

Whether x-ray or radium is used as preoperative therapy, the optimum time interval is placed at around six to eight weeks This allows the inflammatory reaction following radiation to subside and the normal tissue to recover. To delay longer is to run the risk of reactivation of the tumor. With increasing evidence to indicate that tumor cells are stunned rather than killed, there has been increasing agitation to shorten the time between radiation and definitive surgery. With the element of infection reduced and the activity of the tumor cells attenuated, there is logic in the call for earlier intervention. There appears to be little reason other than a misconception of what we are trying to accomplish with radiation to wait for the full effect of radium in the hope that the carcinoma will be destroyed. Randall suggests in support of this contention that the prognosis is probably "more dependent upon surgery than on radiation and may be little influenced by the latter." Arneson finds evidence of recovery of the residual tumor at the end of six weeks and raises the question of why hysterectomy is not done at the end of a week. The standard interval between radiation and surgery in most major clinics, however, remains at six to eight weeks.

SURGERY

BASIC CONCEPT

Since all surgeons interested in cancer are of the opinion that malignant disease anywhere in the body is best removed surgically, it is not surprising that there

for surgery with relation to the above factors, we must decide what we are trying to accomplish. If it is to eradicate the tumor completely within the uterine cavity, if not in the muscle, then a delay in the time interval before surgery is advisable. If, on the other hand, we simply strive for sterilization of the tumor in order to reduce the percentage of implant and lymphatic metastases to the abdominal wall and vagina, then hysterectomy might better be performed at the end of a week. Smith found, for example, that one-half of the cases where full radiation was employed had residual disease when hysterectomy was performed five to 14 months later. Reactivation of the tumor growth seems a likely explanation. Rather than take this risk, early operation short of the six to eight week period would seem to be advisable.

COMPLICATIONS OF RADIATION

Morbidity. While uniform radiation of the endometrial cavity is the goal to strive for, this may be accomplished only with some element of risk if one elects to employ radiation from multiple point radium sources as suggested by the methods of Heyman and Arneson

Perforation of the uterus is not uncommon in attempting to establish a diagnosis with the curet. The stenosed os of the postmenopausal uterus, together with the thinned-out musculature and the soft spots created by tumor invasion, render perforation of the uterus a common misadventure. When an attempt is made to dilate the canal of such a uterus to the point where it may be adequately packed with radium-containing capsules or the radium ring, or the other devices designed to radiate the entire canal, the risk of perforation rapidly mounts Heyman speaks of perforation of the uterus as inevitable Among 93 cases treated by Arneson, 2 instances of perforation were noted, requiring laparotomy in one to recover a lost radium tube Kaplan speaks of incising the internal os for a depth of ⅛th inch in order to allow ease of applicator and removal of the radium ring Perforation of the uterus then is a not uncommon complication both in making the diagnosis and in instituting treatment.

The extent of morbidity varies in relation to the stage of the disease and the degree of differentiation of the pathology. The more advanced the disease with increasing infiltration of the muscle wall, the greater the morbidity Fricke and Bowing found that only 60 per cent of their patients among the 65 grade IV cases could complete their divided dose treatment because of such complications as pyometritis, phlebitis, pelvic cellulitis, bacteremia, and subdiaphragmatic abscess Actually the percentage morbidity was high for the entire group treated by radium irrespective of the extent of the disease The entire 109 cases had a morbidity of 9 per cent.

The morbidity following radium alone is distressing but in most instances serious only in that it is impossible to complete the full course of treatment such as Fricke employs in his divided dose method This is reflected in his salvage figures where 28 per cent five year results from the limited treatment indicates a decline of 10 per cent from those of the entire group. Where a single treatment of intracavitary radiation is given the morbidity must be accepted. An increased morbidity may be anticipated when intracavitary radiation supplements x-ray therapy but this increase may be justifiable from the added hope of salvage

vaginal operation. When the abdominal approach is employed, the liver may be palpated for metastases, the operation discontinued, and radium given. This possibility is manifestly out of the question if the vaginal route is employed. The patient is committed to vaginal extirpation in the presence of undetectable distant metastases. Extension of the disease to regional nodes is amenable to treatment by the abdominal operation but denied to the vaginal method. The presence of associated pathology such as fibroids or ovarian pathology may greatly complicate the removal from below. In fact, most surgical problems encountered in hysterectomy for endometrial carcinoma can best be managed through the abdomen. The chief disadvantage lies in the great difficulty that may be encountered in removing the adnexa. Metastases to the ovary and tube occur infrequently yet often enough to suggest that failure to remove them must be classed as an incomplete operation. Masson and Gregg believe that the poor risk patient with a small tumor in a prolapsed uterus may be attacked by the vaginal method but otherwise an abdominal hysterectomy is the treatment of choice.

Supravaginal Hysterectomy

Supravaginal hysterectomy must be classed with vaginal hysterectomy, without removal of the tubes and ovaries, as an incomplete operation. Unless unforeseen difficulties are encountered during the operation which make it imperative to curtail the surgery, it may be categorically stated that there is no place for supravaginal hysterectomy in the treatment of carcinoma of the endometrium. To be sure, some cases of fundal cancer have been cured by supravaginal hysterectomy, but there are many more where the disease remains or recurs in the cervical stump or upper vaginal vault Total hysterectomy, regardless of its technical difficulties, is thus essential unless the surgeon is willing to accept an incomplete operation for malignant disease. No surgeon will recommend supravaginal hysterectomy for carcinoma of the fundus as anything but a poor compromise.

In the majority of instances, supracervical hysterectomy has been performed in complete ignorance of the fact that carcinoma is present within the uterus. The pathologist is the first to make this discovery. This frequently leaves the surgeon with the problem of handling both the retained cervix and the adnexa as well The operation should be performed within the month according to Meigs, when one or both have been left behind.

Practical Considerations. There are several good practical working rules which, when employed routinely, will avoid this tragic misadventure. In the first place the unsuspected finding of carcinoma within the uterus is an excellent reason for performing a preliminary curettage on every case where hysterectomy is contemplated This would appear to be axiomatic but is more often neglected The very case regarded as clear-cut, where curettage can be dispensed with, is apt to be the case in which disaster occurs. As a further safeguard every uterus removed whether supravaginally or totally should be opened and inspected at the operating table before the abdomen is closed. Not infrequently where curettage has been performed carcinoma may be found undetected in the cornua of the uterus The routine practice of inspecting the open endometrial cavity will avoid the unfortunate experience of leaving the adnexa or cervix in the presence of unsuspected malignancy. To those who recommend total hysterectomy whenever the uterus is to be removed, the not uncommon experience of finding

is nearly unanimous agreement that complete hysterectomy with removal of both tubes and ovaries is the treatment of choice. The relatively slow growth of lesions which are generally of low grade malignancy occurring within the heavy muscle walls of the uterus are factors contributing to the logic of such a procedure. As noted, radium is given as a preliminary step to sterilize the tumor as far as possible, in order to reduce the risk of dissemination of cancer cells by implant or lymphatic extension when surgery is performed Whenever the patient's general condition is such that the thought of surgery can be entertained, the entire uterus and its adnexa should be removed

As regards the use of preoperative radiation it is evident that the aim has not been to eradicate the primary carcinoma within the uterus. Following radiation certain sensitive tumors will seem to have vanished, but this should not be taken as evidence that surgical removal is not the basic part of the planned treatment. As Behney insists, the removal of the uterus must be performed on all patients regardless of how well they appear to have responded to radiation. The removal of the entire uterus is the only way by which we can be sure of the extension of the disease beyond the uterine cavity.

Total Hystrectomy Including Adnexa

The entire uterus must be removed. As already noted, the carcinoma may arise low in the endometrial cavity or extend down into the cervix from a growth primarily situated high at the top of the fundus. Moreover the longitudinal lymphatics situated within the uterine wall extend downward to include the cervix and the upper vaginal wall. The disease then is potentially one of the entire uterus Likewise the lymphatic spread may take place to the ovary and tube which should be removed regardless of an innocent appearance. One may be tempted to leave ovarian tissue behind when the disease is discovered in a relatively young woman Regardless of the size of the primary tumor, such a considerate attitude cannot be condoned In addition to the possibility of metastases to the adnexa one must consider the advantages to be gained by surgical castration Ovarian hormone stimulation has been discussed in relation to etiology. Castration has proved of value in breast carcinoma both as prophylaxis against recurrent disease as well as for the effect on known metastases in lung and bone. The same effects may be anticipated in carcinoma of the endometrium There is increasing evidence that the best results from treatment are obtained when x-ray treatment is given following preoperative radiation and surgery. There is little, therefore, to recommend ovarian conservation in this disease

Abdominal Hysterectomy

As Novak observes, there are but few dissenters at the present time to the accepted theory of total abdominal hysterectomy with bilateral salpingo-oophorectomy six to eight weeks following preliminary radiation Meigs found that 14 of 16 authors discussing the treatment of carcinoma of the fundus preferred the abdominal approach, while 3 chose the vaginal route.

Vaginal Hysterectomy

The disadvantages of vaginal hysterectomy are obvious. It is almost impossible to remove the various extensions of carcinoma beyond the uterine cavity by the

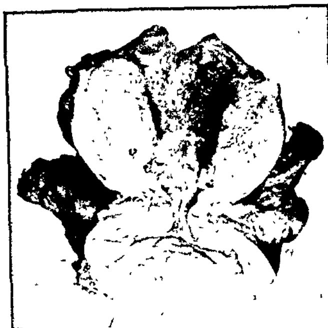


FIG. 47.—Adeno-acanthoma. Positive nodes are found along the common iliac and obturator areas. Note the location of the primary tumor near the endocervix.



FIG. 48.—Adeno-acanthoma, specimen removed at exenteration. Total hysterectomy had been performed four years previously.

unexpected malignancy is an added reason for employing this method rather than supravaginal hysterectomy. If the adnexa are retained the uterus must also be opened before closing the abdomen.

Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy

The technic for performing total hysterectomy with bilateral salpingo-oophorectomy has been adequately described in the textbooks and literature and will not be repeated here.

Practical Considerations. Catheterization of Bladder and Ureter: If it appears from the general configuration of the patient that the operation may be prolonged it is well to insert a Foley type of inlying catheter attached by tubing to a drainage bottle beneath the operating table. In our experience it has not been necessary to insert ureteral catheters. There is no feeling against the use of ureteral intubation except the impression that they are not essential to successful management.

Closure of the Cervix: Closure of the cervix with heavy interrupted silk sutures is considered a good technical maneuver designed to prevent spillage through the cervical canal Implant metastases on the fresh vaginal wound may thereby be minimized

Ligation of the Tubes For the same reasons of spillage to prevent soiling of the cul-de-sac or abdominal incision with tumor cells expressed through the open tubes, Sampson, Randall, and Counseller recommend ligation of the tubes as an initial procedure in the laparotomy.

Handling of the Uterus Likewise it is axiomatic that a tenaculum should not be placed upon the fundus of the uterus for fear of possible dissemination of malignancy Commonly clamps are placed along either side of the uterus along the broad ligament Counseller recommends that the uterus be handled gently, using gauze over the fundus, as traction is maintained by hand rather than by clamps

General Considerations. Evidence of Distant Extension: Before electing to continue with the removal of the uterus, the surgeon should palpate the liver and the periaortic and pericaval nodal areas for evidence of extension of the disease beyond the uterus If positive nodes are evident this high or liver metastases are extensive then the operation may be discontinued and radium treatment given. The mere palpation of the nodes along the aorta is not proof that disease has extended this far, for the nodes are frequently inflammatory. There must be microscopic evidence of disease before abandoning the surgical procedure Likewise a solitary liver metastasis is not enough to discontinue surgery.

Regional Extension The regional nodal areas are palpated for possible extension of the disease to the iliac and obturator nodes. If disease is palpated in the parametria or involves the serosa such an extension is possible.

Johnson has advocated bilateral pelvic lymphadenectomy as a regular part of the hysterectomy for endometrial carcinoma Ward suggests that when the cervix *and fundus are both found to be involved with cancer, the radical Wertheim* operation with bilateral pelvic lymphadenectomy is indicated for carcinoma of the endometrium, as it is for the cervix Disease involving the cervix might be expected to follow the same pathways as epidermoid cervical carcinoma. Two recent cases, one of adeno-acanthoma, proved to have obturator metastases when

endometrium. The operation is completely inadequate as a cancer operation. If the glands are not to be dissected, at least the ureters should be isolated and the uterine vessels ligated at their point of origin from the hypogastric artery. The bladder with ureters identified should be advanced downward so that an adequate section of parametrium may be removed together with a more adequate vaginal cuff. Burman, Corscaden, and Arneson all comment on the frequency of parametrial extension and vaginal metastases. Corscaden believes that there is an intimate relationship between the uterine and vaginal lymphatics to account for the frequency of vaginal metastases. Arneson believes that 40 per cent of adenocarcinomas of the endometrium have extension of disease outside the volume of tissue removed surgically. The literature abounds in discussions of the improved methods of preoperative radiation. The results are improved when followed by "adequate surgery." Unfortunately the adequate surgery is a simple total hysterectomy differing not at all from that performed for benign disease. One may justifiably question the classification "adequate." With the common employment of fluid and blood replacement, plus the use of the antibiotics and improved anesthesia, more radical surgery is possible without increased risk even in the obese patient who has endometrial carcinoma.

Postoperative Roentgen Treatment. The same arguments advanced for more extensive surgery may equally well apply to the use of x-ray treatment in the postoperative period. With the aim in therapy directed toward individualization rather than standardization, x-ray should not be used routinely. The roentgen ray in sufficient doses to be cancerocidal in obese patients is not without its hazards. Counseller believes that surgery alone is all that is needed for the low grade lesions Schmitz observes, however, that it is not always possible to determine clinically the extent of the disease and frequently when hysterectomy is performed the ramifications of the tumor are more widespread than originally supposed It would thus perhaps be more logical to perform the hysterectomy immediately upon receipt of the diagnosis of cancer. When evidence of extension of disease beyond the uterus is encountered, x-ray treatment should be recommended This is in keeping with the views expressed by Payne, Ward, and Randall who feel that in operable cases the disadvantages of preoperative radiation through delay in the time for definitive surgery outweighs the advantages. Excellent results are reported by Kamperman, Smith, Miller, and others from the routine use of preoperative radiation, surgery, and subsequent roentgen radiation Perhaps, as Randall suggests, the improved results may be due to the surgery and x-ray rather than the preoperative radiation. The tabulation of combined statistics from all clinics employing preoperative radium and surgery shows actually but little improvement over those cases treated by surgery alone, except in reports from individual clinics or isolated small groups of cases.

Treatment of Vaginal Metastases. Some measure of the effectiveness of preoperative radiation may be checked by the consideration of the number of vaginal metastases developing after treatment Smith found that whereas 6 3 per cent of patients who were treated surgically without radiation developed vaginal metastases, 5 6 per cent did so after preoperative radiation Again this would throw some doubt on what we consider as adequate surgery. Of the 24 cases

regional node dissections were done. We are in agreement with Johnson that wider sections of the parametrium and vagina are possible when this procedure is added. It is not generally practiced and perhaps the increased morbidity and mortality in older more obese patients may outweigh the value of nodal dissections as a routine part of the operation. At any rate the possible sites of nodal metastases should be palpated and appropriate action undertaken.

Operative Mortality. The operative mortality for carcinoma of the endometrium as compiled from the literature ranges from 4 to 7 per cent. Most of this mortality appears among the earlier cases in any series before the advent of antibiotics and the era of repeated blood transfusions. Masson and Gregg reporting a mortality from total hysterectomy of 4.5 per cent, believe that in the present day the mortality should not exceed 2 per cent The majority of cases died of peritonitis, pneumonia, or cardiovascular accidents secondary to embolism. All three conditions have acquired some measure of effective control. The use of preoperative radiation should further reduce the incidence of sepsis

Operative Morbidity. No appreciable technical difficulties appear to have been created by the preoperative use of radiation and it would appear that except for mild cystitis and proctitis no postoperative complications are traceable to its use The abdominal wound as well as the vaginal incisions appear to heal equally well whether the patient has been previously x-rayed or not Occasionally superficial femoral vein ligation has been necessary, either as a prophylactic against the development of emboli or as a preventive measure following a sublethal embolus. Damage to the ureter need not be, yet occasionally is, followed by ureteral fistula or frank hydronephrosis if the ureter is either sectioned or ligated Ureteral vaginal fistulas frequently repair spontaneously. Some infection may develop both in the abdominal wound and deep pelvic tissues, particularly when the patient has concomitant diabetes Such infections are seen less frequently with the widespread use of chemotherapy.

Discussion This constitutes the operation considered as adequate surgery for carcinoma of the endometrium With the preoperative use of radium and the fact that the majority of carcinomas of the endometrium are still confined to the uterus, such surgery may well be adequate for most of the cases with carcinoma of the endometrium The radiologists are far from satisfied with their technics for giving radium and x-ray. Certainly we are not in agreement with Heyman who believes that surgery has reached the peak of perfection and that any improvement in the results for carcinoma of the endometrium will come through improvement in radiologic technics There is no reason for the surgeon to be complacent about the surgery for carcinoma of the fundus Actually, the routine operation commonly employed is exactly the same procedure that we use for a benign fibroid. In how many cases positive glands will be found is debatable and perhaps routine dissection of the iliac and obturator areas is not justifiable However, when carcinoma of the endometrium recurs, it is apt to do so in the parametrial and paravaginal areas, with involvement of the vaginal vault appearing in about 6 per cent of the cases whether radium is used preoperatively or not. Meigs found it in 12 per cent of his series. It is obvious that not enough parametrium or paravaginal tissue is being included in the routine operation for carcinoma of the

massive recurrence in the posterior vaginal wall. The cervix proved to be free of disease. This patient is alive without recurrence, one year after the operation. The second had such minimal disease that the primary lesion could hardly be detected when an "adequate" operation was done two years before. Massive recurrence developed. The lymphatics and residual parametria were infiltrated with disease. The third had had multiple recurrences throughout the vaginal mucosa.

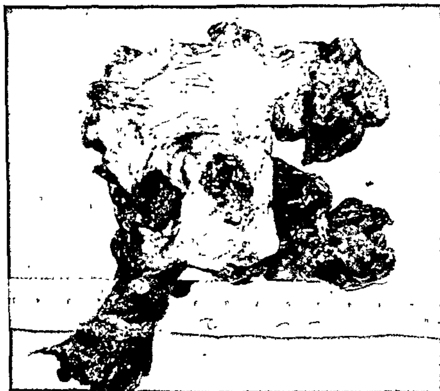


FIG. 50 —Total vaginectomy, recurrence two years after total hysterectomy. The primary tumor was minute at the time of hysterectomy

Perhaps the best prophylaxis against recurrence of disease in the parametria or vagina is not radiation but a more adequate primary dissection at the time of the definitive surgery.

PROGNOSIS

Because neoplasm of the endometrium exhibits a relatively slow growth, is confined within thick muscle walls, and has a tendency to metastasize late in the course of the disease, the prognosis in general may be regarded as favorable. With an operability rate of about 70 per cent, the over-all cure rate for all cases seen in any given series should better 50 per cent

There are many factors bearing on prognosis which must be considered in proper evaluation of the potentialities of the disease The general condition of the patient has a direct bearing on the outcome in that it influences not only the type of treatment utilized but the actual results obtained from the chosen form

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among a series of over 300 reporting for re-treatment, 15 out of 16 treated with surgery, or radium, or radium and surgery had vaginal metastases. Only one of the 24 was permanently cured.

Fricke, Heyman, Smith, Miller, Arneson, and others devised various forms of local radium treatment to be employed before and after surgery in the endeavor to cut down the incidence of vaginal recurrences The chief reliance must be



Fig 49—Total vaginectomy (abdominal) Recurrence in vagina 18 months after supravaginal hysterectomy Cervical stump is free of disease, lymphatic infiltration

placed on these methods of applying radium locally plus the use of interstitial platinum-covered radium needles or the intravaginal cone method of delivering x-ray treatment While the prognosis from such secondary manifestations is, by and large, poor, they may represent the only manifestation of recurrent disease as noted by Ackerman Treatment is therefore indicated The size of the dosage cannot be standardized and must by its very nature depend on the size and location of the individual metastasis.

Inasmuch as the recurrence in the vagina suggests lymphatic infiltration, there are definite disadvantages in treating each solitary recurrence as it manifests itself Though the procedure is not recommended, 3 recent cases were subjected to total vaginectomy. The findings have more application to the discussion of more extensive primary surgery than to the treatment of the vaginal recurrence One patient had a supravaginal hysterectomy 18 months before she developed a

not of the associated pathology. The symptoms may be masked by the presence of fibroids or continued hormone therapy.

In the reproductive period the chief symptom of bleeding is all too frequently attributed to the presence of a fibroid. The duration of symptoms in patients with carcinoma and fibroid is, according to Norris and Dunne, four times as long as for the group as a whole. In the postmenopausal group, on the other hand, hormone therapy and minimal nature of the symptoms without pain may tend to prolong the period before definitive treatment. Inasmuch as the disease is slow growing, it may appear anywhere from one to 25 years after the menopause. The role of the duration of symptoms in this group is therefore difficult to appraise. Scheffey noted that the time wasted before definitive treatment was twice as long in the postclimacteric period as in the premenopausal epoch.

One might expect that pain, which is usually absent except in the late stages of the disease, could be regarded as an index of the extension of the disease beyond the uterus, and therefore indicate a poor prognosis. But Murphy found only 16 cases among 56 who had pain as a major symptom where the disease actually extended beyond the uterus, and conversely 43 cases where extension was proved had no pain at all.

Meig's conclusion that the duration of symptoms has little bearing on prognosis would seem to be confirmed.

Grade of Malignancy

Inasmuch as the final grade of tumor can be assayed only after the uterus has been removed, the microscopic evidence of the degree of malignancy determined at the time of curettage has little bearing on the type of treatment proposed. If we could determine that the lesion was of low grade malignancy then early operation, without the time loss entailed in the use of preoperative radiation, would provide the 90 per cent five-year survival anticipated by Healy. Since the majority of lesions are either grade I or II and are said to be radiation-resistant, this would be of great importance. However, as Randall notes, the microscopic evidence from curettage gives a false indication of the true nature of the tumor, for the degree of maturity appears higher in curetted material than from the sections of the same tumor where invasion of the wall has occurred As a result the type of treatment chosen is based on other factors than the grade of malignancy. It is a common observation that specimens from different parts of the same tumor may show different degrees of differentiation It is necessary therefore to have the entire tumor at hand before evaluating prognosis on the basis of microscopic grading

All authors agree with Murphy that there is a definite decrease in life expectancy which can be traced to the loss of structural differentiation The higher the degree of malignancy and the more undifferentiated the tumor, the graver the prognosis Where the squamous element enters the pathologic picture (about 11 per cent), the percentage of cures drops off sharply when radiation is employed. In our experience the true adeno-acanthoma case is never cured by radiation. With lesser degrees of squamous cell proliferation, Fricke and Bowing secured 17 per cent of five year cures from radiation The results from surgery, however, are only slightly less than for adenocarcinoma. Where the tumors have

of therapy. If all cases dying of intercurrent disease are to be classed as dead from cancer for which they were treated, then in this older age group, associated with a high percentage of patients with obesity, hypertension, and diabetes, the deaths from complications traceable to these associated diseases may reduce the salvage figures as much as 20 per cent according to MacLennan.



Fig 51 —Total vaginectomy, the small rounded areas represent multiple recurrences following total hysterectomy for carcinoma of the endometrium There was a history of repeated radium treatments

The main factors bearing on the prognosis from malignant disease in general apply also to the life expectancy from carcinoma of the endometrium The duration of symptoms, grade of malignancy, extent of the disease, and type of treatment must be considered before venturing to offer a prognosis in any one individual patient

Duration of Symptoms

Inasmuch as there is marked individual variation in the clinical behavior of any two tumors of comparable pathology and extent of growth it is difficult to assay truly the part played by duration of symptoms upon longevity. The disease may be of long duration and bulky in character yet be amenable to treatment A small growth may invade and metastasize early, while a large growth may give no early symptoms It is difficult to determine and the history may be misleading as to just when the primary symptom of bleeding becomes a symptom of carcinoma and

may behave differently in different individuals and that there may be complex variables in tumor growth which are more important factors in the end result than mere extension of the growth. The life span of two different tumors of the same extent may be different.

Though the different classification devised to evaluate the extent of the disease in relation to prognosis are obviously but clinical appraisals, nevertheless there appears to be a definite relationship between the extent of the disease, based on the size of the uterus and the prognosis All authors are agreed that the smaller uterus gives the better prognosis. Healy feels that a uterus the size of a two months' pregnancy should be a favorable case for five year salvage regardless of whether radiation is used or not, provided the surgery is adequate. Corscaden obtained a 75 per cent five year survival when the uterus was smaller than a two months' pregnancy, but only 37 per cent when the uterus was further enlarged, and only 5 per cent when extension was noted beyond the uterus.

Scheffey attempted to simplify the classification by dividing the patients into two groups depending on whether the disease appeared to remain confined to or extended beyond the uterus. The so-called A group was confined to the uterus, while the B group had clinical evidence of extension outside the uterine cavity. The resultant figures bear a striking resemblance to those of Healy and Brown, Miller and Henderson, and Fricke and Bowing whose classification appears more elaborate and cumbersome. Scheffey found 74 per cent of the entire group were in the primary A classification compared to 71 per cent for Healy and Brown and 69 per cent for Miller and Fricke. The accuracy of the more advanced stages of the disease is more readily attested than that confined within the uterus. Direct inspection of the vagina may detect vaginal extension while a rectal examination is fairly accurate in differentiating broad ligament fixation from malignant disease in contrast to that present in pelvic inflammatory disease or endometriosis

Fricke and Heilman find a definite relationship between the type of treatment and staging of the disease in evaluating prognosis. Thus while 100 per cent of the grade I cases treated by surgery survive five years, only 50 per cent were salvaged by radium In grade II cases the results from radium and surgery are about equal while in the advanced cases more of the radiated patients survive

It may then be stated that however inadequate the classification of the stage of the disease may be, it is nevertheless a clinical fact that the extent of the disease is the most important single prognostic factor other than the actual type of treatment employed.

Type of Treatment

Before attempting to compare the end results of one type of treatment as opposed to another it is important to be certain that the data from which conclusions are to be drawn are actually comparable. For example, it has been the habit of surgeons in this country to reserve radiation therapy for those patients who through age, weight, general condition, or extent of disease have been considered as unsuitable for surgery. Any consideration of the effectiveness of radiation in comparison with the result to be *obtained* from surgery would be manifestly unfair to radium if results alone are to be taken as the measure of

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Though the different classification devised to evaluate the extent of the disease in relation to prognosis are obviously but clinical appraisals, nevertheless there appears to be a definite relationship between the extent of the disease, based on the size of the uterus and the prognosis. All authors are agreed that the smaller uterus gives the better prognosis. Healy feels that a uterus the size of a two months' pregnancy should be a favorable case for five year salvage regardless of whether radiation is used or not, provided the surgery is adequate. Corscaden obtained a 75 per cent five year survival when the uterus was smaller than a two months' pregnancy, but only 37 per cent when the uterus was further enlarged, and only 5 per cent when extension was noted beyond the uterus.

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It may then be stated that however inadequate the classification of the stage of the disease may be, it is nevertheless a clinical fact that the extent of the disease is the most important single prognostic factor other than the actual type of treatment employed.

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Before attempting to compare the end results of one type of treatment as opposed to another it is important to be certain that the data from which conclusions are to be drawn are actually comparable. For example, it has been the habit of surgeons in this country to reserve radiation therapy for those patients who through age, weight, general condition, or extent of disease have been considered as unsuitable for surgery Any consideration of the effectiveness of radiation in comparison with the result to be *obtained* from surgery would be manifestly unfair to radium if results alone are to be taken as the measure of

been graded and the pathology considered in relation to longevity, approximately 90 per cent of the grade I and II lesions survive five years. As the grade rises the survivals decrease The medium malignancy group salvage about 65 per cent while the higher degrees of anaplastic growth result in cures at five years in about 50 per cent. Where radiation is employed as the sole treatment the survival figures are somewhat lower Fricke and Bowing obtain 39 per cent for grades I and II, dropping to 25 per cent for grade III, and 12 per cent for grade IV The figure 39 per cent rather belies the previous conception that the low grade lesions are radiation-resistant. The higher grades of malignancy with less well-differentiated cells might be expected to be more highly sensitive to radiation and give a higher percentage of cures. That cures are not forthcoming is perhaps due to the likelihood of earlier distant extensions in the more rapidly growing tumors As Arneson also suggests, there is a great difference between radiation sensitivity and curability There is general agreement that histologic grading, at least as far as radiation is concerned, has less significance than is apparent in surgery, where the lower grades of malignancy give a better prognosis than the medium grades, and the latter improved results over the more undifferentiated forms of carcinoma

Extent of the Disease

The classification of the extent of malignancy is much more difficult to determine for carcinoma of the endometrium than for cervical malignancy. A variety of schemes has been suggested, based on the enlargement of the uterus and a clinical estimate of the degree of extension beyond the uterus It is obvious that any attempt to base the prognosis on such findings can be at best but an approximation This is particularly true where the classification is based on the size of the uterus. At the time of diagnostic curettage and pelvic examination under an anesthetic the size of the uterus may at times be accurately outlined in the obese abdomen but neither the size of the uterus nor the depth of the cavity gives accurate information as to the extent of the primary lesion nor the amount of infiltration of the tumor wall. Healy and Brown, Crossen, Ward, and Schmitz all have classifications based on the size of the uterus and the depth of the cavity. The presence of associated fibroids or adnexal pathology of benign nature may alter both the size of the uterus and the degree of fixation Likewise a large growth may be present in the cavity, enlarging and distending it without invading the uterine wall The prognosis from this extent of malignancy may be better than the small primary tumor which invades the wall and presents at the serosal surface Moreover the latter may be a more difficult technical surgical problem than the larger and more distended uterus.

Miller, in addition to grading the stages of the disease on the basis of the size of uterus and the depth of the cavity, further modifies the classification by the microscopic findings at the time of hysterectomy. Of the 39 cases treated more than five years before, 83 per cent of the grade I, 75 per cent of grade II, and 61.5 per cent of grade III patients survived Inasmuch as preoperative radiation may destroy the evidence of the extent of the primary tumor, it is again difficult to determine the magnitude of the original involvement even when the uterus has been removed Arneson feels that the same grade of tumor

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	Surgery	*Radium and Surgery*	*Radium or X-ray*
Total cases	124	89	127
Five year salvage	58.8 per cent	65.2 per cent	25.2 per cent

An explanation of the poorer results from radiation than is generally acquired may lie in the fact that the clinic is surgically minded and only the poorest risks are subjected to radiation. The radiation technic is also open to criticism in that the single application employed in this clinic has been proved elsewhere to be less effective than other methods which give a more homogeneous radiation. Heyman for example has treated 354 patients between 1914 and 1933 with a single linear application with a relative cure rate of 44.6 per cent. In 1933 the technic of packing the uterus with multiple small radium capsules was introduced in order to obtain a more uniform radiation of the entire cavity. 316 patients were so treated from 1934 to 1939 with a 61.9 per cent five year survival. Inasmuch as radiation is the treatment of choice in this clinic there is less operative interference and the two series may be regarded as unselected and suitable for comparison. The 17 per cent improvement is directly traceable to radiation technic. Arneson employing a similar technic obtained only 22 per cent salvage from radium alone with single applicator, but 32 per cent with packing. The results from radium and hysterectomy were 54 per cent for the single tandem applicator and 79 per cent after packing the uterus with radium capsules.

Discussion

The compilation of end results does not indicate an outstanding improvement in the results obtained from preoperative radiation when considered in bulk, though smaller series such as Arneson's are encouraging. It is probable that more advanced cases are now being included in the operable group, though the same explanation applies to those treated by surgery alone. Taylor and Becker made note of an encouraging trend when, in their series of 119, hysterectomies followed a preoperative radiation course of 3600 mg. hours, the end results were found to be 44.1 per cent for the entire group but increased to 73.8 per cent when no residual tumor was found in the uterus. Arneson noted a similar percentage difference and believes that persistence of carcinoma after radiation is more important in prognosis than size of lesion or grade. Inasmuch as Stowe believes that a rare series of preoperatively radiated uteri will show more than 50 per cent of the tumor destroyed, this difference in survival rates is most important Taylor postulates that the difference in effect may be due to the effect on the more distant tumor cells But, as Randall observes, if radiation is to be effective in eradicating disease in areas not ordinarily approached surgically, such as the trigone area of the bladder and the distant parametria, then the radiation should be given as in cancer of the cervix. The complications of surgery following such intense radiation may increase the morbidity and mortality in these obese patients to the point where no improvement will be noted in the over-all cure rate This again brings up the question of what we mean by adequate surgery. Whether preoperative radiation is given or not the same technic employed for benign disease of the uterus cannot by any standard be considered as adequate for malignant disease. Whether or not the regional nodes should be dissected, as suggested by Johnston, is debatable, but certainly in

success or failure of the treatment. Likewise enthusiastic reports appear in the literature of the improved salvage figures to be obtained by the preoperative use of radium in comparison with those from surgery alone. Again the data are not comparable Actually surgical conditions today are not what they were 15 years ago The drop in operative mortality from total hysterectomy with removal of the adnexa would practically balance the improvement in salvage figures noted from the use of preoperative radiation With the modern adjuncts to surgery such as blood and fluid replacement, improved anesthesia, and chemotherapy, better results from surgery could be anticipated in cases of comparable extent of disease and general physical condition. The results of surgery of 15 years ago are being used as a basis for comparison with the results obtained today. Moreover total hysterectomy 15 years ago was not the procedure of choice for all pathology requiring hysterectomy as it is today The familiarity with the technical details of the surgery was limited to the experience to be gained from the infrequent case of carcinoma of the endometrium. With the experience gained from total hysterectomy for benign disease, the results from surgery alone would obviously be improved over those of 15 or 20 years ago. Conversely, with increased familiarity with the technical details and the newer additions to surgical armamentarium, more advanced disease in poorer risk patients is being subjected to preoperative radiation and surgery. If the results obtained from preoperative radiation and surgery do not indicate an outstanding increase in salvage, part of the explanation may be traced to such a cause.

Inasmuch as it takes about 10 years to collect a series of cases of carcinoma of the endometrium of sufficient magnitude to be statistically important for end result study, the larger series reported deal with experience prior to 1935, while the smaller sporadic groups of less statistical validity deal with the experience in treatment since that time This explains in part the marked variation in the results obtained from preoperative radiation and surgery.

An attempt has been made to compile from reports in the literature through 1948 end results from the use of surgery alone, surgery plus radium, and radiation alone.

	Surgery Alone	*Surgery Plus Radiation (Various combinations of surgery, radium, and x-ray)*	*Radiation Alone (Radium alone or radium plus x-ray)*
Total cases	1,384	1,230	2,387
Five year salvage	63 7 per cent	60 3 per cent	38 per cent

It is interesting to compare these figures with a similar compilation from the literature reported by Arneson in 1936.

	Surgery	*Surgery Plus Radiation*	*Radiation*
Total cases	937	91	998
Five year salvage	57 per cent	60 per cent survival	37 per cent survival

Comparing these results with our own experience gathered from the Massachusetts General Hospital and the Pondville Hospital, Massachusetts Department of Public Health, a striking similarity is apparent.

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view of the location of the late metastases in the parametrial area and vagina one may argue for a more complete dissection at the time of the original surgery. Pemberton and Smith, Masson and Gregg, and Miller note a 13 per cent drop in the salvage rate between the fifth and 10th years Miller believes that 71 per cent of the late deaths are due to carcinoma The difference then is not all traceable to intercurrent disease. There appears to be sufficient reason to view critically the type of surgery we are employing routinely for carcinoma of the endometrium, regardless of the radiation supplement or when it is employed.

There are two outstanding series in the literature which give an optimistic prognosis for the treatment of carcinoma of the endometrium in the future. Heyman, employing the packing technic for radiation of the endometrial cavity, secured a 66 per cent survival at five years among 153 cases considered operable. Where radiation was believed to have failed, 13 additional cases were later subjected to surgery increasing the survival to 75 per cent This would seem to indicate that radiation properly given may be expected to do as well in the operable cases as surgery Whether this experience can be repeated universally throughout the world clinics is questionable. Miller employing preoperative x-ray followed in six weeks by surgery salvaged 77 per cent of five year cures among the so-called favorable or operable group. Unfortunately this group represents only 30 per cent of the total seen. Where the same technic is applied to the advanced cases the salvage is only 28 per cent For the entire group of 322 patients seen the five year salvage of 60 per cent is reported, with, as in most series, about 10 per cent too far advanced for any treatment. Though these figures are commendable and give a hopeful tinge to the possibility of longevity, the same 12 per cent decrease is noted in the 10 year survivals when only 65 per cent are found to be alive

It would appear that the addition of radiation both preoperatively and postoperatively is a valuable addition to the surgery as now performed The number of vaginal and parametrial recurrences together with the 12 per cent difference in salvage rates between the fifth and 10th year would seem to indicate that we must devote some of our interest in the proper treatment of carcinoma of the endometrium to the subsequent surgery as well as to the improved technics in radiation.

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Nontuberculous, Nongonorrheal Infections of the Urinary Tract

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Nontuberculous, Nongonorrheal Infections of the Urinary Tract

RICHARD CHUTE, M.D.

GENERAL ETIOLOGIC CONSIDERATIONS

There are several routes by which infecting bacteria may enter the urinary tract. Bacteria are not infrequently introduced into the bladder, and occasionally into the kidney, in the course of instrumentation such as catheterization, cystoscopy, etc. Also the bladder occasionally becomes infected by the upward extension of an acute urethritis or acute prostatitis. Another route by which bacteria commonly enter the urinary tract is via the kidneys, to which they have been brought by the blood stream from some focus of infection elsewhere in the body. Such foci may be inflammatory catarrhal conditions of the mucous membranes such as acute upper respiratory infections or acute gastro-enteritis, abscessed teeth and the transient bacteremia which sometimes follows their extraction, infections of the tonsils, middle ear, gallbladder, appendix, or of the blood stream itself (septicemia). From such foci bacteria frequently invade the blood stream and thus are brought to the kidney. Undoubtedly bacteria are thus frequently brought to a normal kidney, but are eliminated through this normal kidney and the rest of the urinary tract, if it is normal, without gaining a foothold and creating an infection However, if the bacteria brought by the blood to the kidneys are either extremely virulent or are in overwhelming numbers, an infection will result, even in the case of healthy normal kidneys, and such an infection will be bilateral. When the bacteria are in smaller numbers or of less virulence, the question of whether or not they will cause an infection, and if so, which kidney or part of the urinary tract will be affected, is determined by whether or not there exists anywhere in the urinary tract any of the well recognized conditions—which will be mentioned shortly—which reduce local resistance to infection and thus predispose to its occurrence.

If one of these predisposing conditions such as hydronephrosis or residual urine in the bladder is present, an infection of the part affected by it will probably result. This was shown in a striking manner by the experimental work of Mallory and his co-workers. In a series of rabbits they partially occluded one ureter with a constricting ligature, thereby producing hydronephrosis The other kidney and ureter were untouched. Colon bacilli were then injected intravenously and an acute pyelonephritis, similar to that seen in man, was

obstruction, stricture of the urethra occurring anywhere from the bladder outlet to the meatus, calculi in the bladder or urethra, diverticulum of the bladder or urethra, neurogenic "paralyzed" bladder due to nerve trauma or disease, valves of the posterior urethra in children, foreign body in the urethra, and even to a prepuce with a tiny pinpoint meatus While this list includes most of the causes of obstruction and resulting stasis, there are undoubtedly other causative lesions.

STONE

The second commonest factor favoring infection is the presence of stone anywhere in the urinary tract By its constant contact with the tissues a calculus causes continual irritation, foreign body reaction, and minor trauma, which lower the local resistance of the tissues to infection whose occurrence and continuance are thereby encouraged. In addition to this foreign body reaction of continuing trauma, the presence of stone anywhere in the urinary tract is also often associated with a greater or less degree of obstruction and resulting stasis. As is true in the case of stasis, it is virtually impossible to eradicate infection permanently by any means whatsoever in the presence of stone.

TRAUMA AND FOREIGN BODIES

As already pointed out in the case of stone, trauma favors the occurrence and continuance of infection This trauma may be due to the presence of stone or of any other foreign body in the urinary tract—a rubber catheter or nephrostomy or cystostomy tube, for example—or it may be due to more active physical tissue bruising of varying degree due to catheterization of the bladder or ureters, cystoscopy, or dilatation of the ureter or urethra. A different type of trauma may also be produced by chemical irritation from any cause, such as lavage of the bladder by too strong an antiseptic solution, or the renal injury and congestion following the ingestion of mercury bichloride.

Chronicity of infection is a potent factor militating against the permanent cure of an infection. In the case of a chronic infection, for example, a mild but long-standing colon bacillus pyelonephritis, the chronically infected tissues have undergone irreversible changes of chronic inflammation and subsequent fibrosis, and seem to have lost their vitality and to have become accustomed to their chronic infection which they are unable to throw off completely, even with the aid of the most powerful modern drugs and antibiotics

Thus there are three factors which favor both the occurrence and continuance of infection: stasis, stone, and trauma, and a fourth factor, chronicity of infection, which often stands in the way of a permanent cure.

CLINICOPATHOLOGIC CONSIDERATIONS

Once an infection occurs in any part of the urinary tract it may well spread to another part of the tract, if not quickly cured, especially if any of the beforementioned predisposing factors are operative For instance, a man with a large residual urine due to prostatic obstruction, which has become infected subsequent to numerous catheterizations, is apt to develop pyelonephritis, the infec-

produced in the obstructed kidneys in about 75 per cent of the animals. Pathologically the acute lesions were found to arise from interstitial abscesses starting around clumps of the bacteria in the small blood vessels and also as a result of organisms passing through the glomeruli into the tubules. It was significant that in the unobstructed kidneys extensive pyelonephritis was never found. More evidence in this direction is furnished by Bell who has found that about 90 per cent of the cases of pyelonephritis are associated with hydronephrosis. At this point, it must be mentioned that direct invasion of the urinary tract by the bacteria of the intestine via the lymphatics is claimed by some. However, no truly convincing evidence of this occurrence has been produced, and general opinion is that this seldom if ever occurs.

Thus the occurrence of a blood-borne infection is dependent partly on the number and virulence of the organisms brought to the kidneys, and partly on the local resistance of the kidneys and other parts of the urinary tract to those bacteria Since this resistance is affected so greatly by certain conditions, they are of great importance. Those conditions, which are generally recognized as reducing resistance and thus predisposing to infection, are the presence anywhere in the urinary tract of (1) stasis, (2) stone, or (3) local trauma or congestion.

Stasis

Undoubtedly the commonest condition predisposing to infection is stasis. Probably the reason it is so effective in this respect is the fact that the flow of urine through the organ or region affected is impeded so that emptying is interfered with and residual urine is always present This creates an ever-present reservoir of an excellent culture medium (urine) which constantly invites bacterial growth, and which by its poor drainage favors the continuance of any infection once it has occurred It is a clinical fact that infection, once established, can practically never be permanently eradicated, even with the most powerful modern drugs and antibiotics, until stasis has also been corrected. Another frequent clinical observation is that wherever continual stasis exists, infection is apt to occur sooner or later Lesions associated with stasis in the urinary tract are many and may be found all the way from the upper pole of the kidney to the tip of the urinary meatus. Examples in the upper urinary tract are hydronephrosis secondary to congenital causes of obstruction at the ureteropelvic junction such as valve, stricture, high insertion of ureter into the renal pelvis or aberrant vessel, also hydronephrosis, with or without hydro-ureter, secondary to obstruction caused by renal or ureteral stone, by tumor within the urinary tract, or by pressure from a tumor or mass outside the urinary tract, e g., carcinoma of the cervix or retroperitoneal malignancies, and also the physiologic dilatation of the kidneys and ureters in pregnancy

Other causes of stasis in the upper urinary tract are ptosis of the kidney with kinking of the ureter and resultant obstruction, dilatation of one or more calices of the kidney secondary to obstruction from stone or from stricture of the infundibulum communicating with the pelvis, stricture of the ureter congenital or acquired, congenital megalo-ureter, and ureterocele

Stasis in the lower urinary tract may be due to benign or malignant prostatic

DIAGNOSTIC CONSIDERATIONS AND PROCEDURES

Infection in the urinary tract always gives rise to pus cells and, if acute, sometimes also to red blood cells, thus producing pyuria and now and then some degree of hematuria. Needless to say, the infecting bacteria are present in the urine. In a patient in whom there is a question of an infection of the urinary tract, the urethral meatus should first be examined for a discharge and, if any is present, a smear made on a glass slide and a culture taken if this is feasible. Gram stain of the smear may reveal the type of organism causing the discharge. If there is an acute discharge with no history of recent chemical irritation, as by venereal prophylaxis, and no organisms can be demonstrated by Gram stain of the smear, a special culture should be taken for the "L" bacillus (about which more later). After looking for a urethral discharge, the so-called two-glass voiding test is carried out, if the patient is a male. This consists of having the patient void the first 75 cc. of his urine into one glass, and the remainder into a second glass. In this way pus in the urine originating from the urethra only can be differentiated from pyuria of the bladder urine, since the first glass of the voided urine contains exudate washed from the urethra, while the second part of the voided urine passes through the washed urethra and is representative of the bladder urine. Thus in the case of urethritis without infection of the bladder urine, the first part of the urine will be cloudy, but the second part will be clear. However, in a case where the bladder urine is infected, both first and second specimens will be cloudy. This simple test is of considerable practical value in the differential diagnosis of the source of pyuria in males. If both urines of a two-glass test are cloudy, it is possible that the cloudiness is due to crystals. A portion of each urine is taken and a small amount of 33 per cent acetic acid is added to each. Any cloudiness due to the common "alkaline" phosphatic crystals clears completely, so that whatever cloudiness is left is not due to crystals, with the exception of uric acid crystals which are not dissolved, but which are rare in fresh urine. Needless to say, cloudy urines should be cultured and also their sediments should be checked microscopically for the presence and quantity of the pus cells, red blood cells, and bacteria.

When obtaining the bladder urine of males for culture, it is quite satisfactory to use the second part of the urine voided into a sterile receptacle, rather than resorting to catheterization. On the other hand, when obtaining the urine of females for examination of the sediment or for culture, experience has shown that it is necessary to use a specimen obtained by aseptic catheterization, on account of the unavoidable vaginal contamination in a voided specimen. In the case of a very sick patient, where it is important to start proper therapy as soon as possible, and to avoid 12 to 24 hours' wait necessary for culture growth, an idea of the general type of infecting bacteria may be gained by doing an immediate Gram stain of the fresh urine sediment, preferably centrifuged. If Gram staining is not available or convenient, a fairly accurate estimate of the type of invading bacteria can be made by looking at the sediment of the fresh urine, centrifuged if possible, under the microscope. Motile bacilli in an acid urine are apt to be colon bacilli, while motile bacilli in an alkaline urine are apt to be *Bacillus proteus*

tion having "ascended" from the bladder. Sometimes this is by direct ascent in continuity via the lumen or tissues of the ureter, especially if the ureter is dilated, in which case a direct reflux may be sometimes demonstrated. In some cases, particularly where there is no obstruction in the lower urinary tract or residual urine in the bladder or dilatation of the ureters, it is felt that the route of the infection is probably from the infected bladder to the blood stream and thence to the kidney.

Also in the case of a patient who has contracted a blood-borne pyelonephritis, the infected urine naturally flows down into the bladder, and if this is affected by one of the predisposing factors, such as stasis due to prostatic obstruction, that bladder will become infected. Furthermore, even if the kidney infection clears up, that bladder will remain infected until its own element of stasis has been remedied Another example of infection extending from one part of the urinary tract to another is the fact that frequently an acute anterior urethritis, if unchecked, will extend upward to the posterior urethra, and thence the infection will spread to the prostate and the bladder, and may even extend to the seminal vesicles and down the vas to involve the epididymis. Thus it is that clinically infection of one part of the urinary tract cannot always be considered as a separate disease entity of one organ anatomically separated from the rest of the tract It may well spread, and therefore this characteristic must be taken into account when treating it.

Furthermore not all renal infections are of the same type or produce the same pathologic picture. For example, a hematogenous infection with virulent staphylococci tends to produce acute focal abscesses in the glomerular system of the kidney cortex without involving the pelvis of the kidney, whereas in an ascending pyelonephritis, organisms of the colon bacillus group tend to attack first the pelvis and then to extend immediately into the medullary pyramids and involve the parenchyma The fact that these different types of bacteria tend to produce different types of lesions, plus the fact that these lesions may be modified by different accessory factors such hydronephrosis or stone, also plus the fact that one type of bacterial infection may be superimposed upon the lesions of another type—all these result in pathologic pictures that are complex and varied, although certain main common patterns stand out.

Before the recently awakened interest in the bacteria causing infections of the urinary tract, and the advent of the newer drugs which are now used to combat them, it was generally assumed that practically all infections of the urinary tract were due to the colon bacillus, except those due to the tuberculosis bacillus or to the gonococcus However, it is now realized that although the colon bacillus is the commonest, a considerable variety of organisms may infect the urinary tract, and that different types of renal lesions may be produced by different bacteria, as already mentioned. Also it has been found that all bacteria are not affected similarly by the same antibacterial drugs, but that certain types of infections are best treated with certain agents These considerations have awakened a keen and necessary interest in the bacteriology of urinary tract infections, and identification of the organism or organisms present is now one of the very first steps to be carried out as a guide to the most effective and intelligent treatment.

acute pyelitis, but since the term "pyelitis" indicates inflammation limited to the kidney pelvis, and since this limitation of infection probably never occurs, as it has been found that the parenchyma of the kidney is invariably also involved, this condition is now thought of and referred to as acute pyelonephritis. As already stated, this may be blood-borne from an acute infection anywhere in the body, or may "ascend" from an infected bladder, often one that has recently been operated upon. Also it may follow cystoscopic ureteral catheterization or instrumentation.

Pathology. In acute pyelonephritis of the colon-bacillus type the kidney is swollen and congested, and in the parenchyma there are patchy areas of suppuration, which tend to take the form of tiny round abscesses in the cortex, and of yellow lines of suppuration in the pyramids. The kidney pelvis is reddened and contains pus, and its mucosa is covered with inflammatory exudate. Microscopic examination shows leukocytes in the glomeruli, and the tubules filled with leukocytes and inflammatory exudate from degenerative changes in the tubular epithelium.

Symptoms, Signs, and Diagnosis. Clinically acute pyelonephritis starts with malaise and a sudden high fever, and may be ushered in with a chill. There is moderate leukocytosis. There is pain in the affected kidney, and tenderness and spasm to deep pressure in the corresponding costovertebral angle or to the "Murphy punch" in this region. This latter is a most reliable test of inflammation in and about the kidney, and consists of striking the costovertebral angle a light blow with the heel of the clenched fist when the patient is in the sitting or standing position If there is inflammation present, the jarring of the blow causes the patient to wince from pain in the kidney, whereas if there is no inflammation the light blow causes no discomfort. The difference in this respect between the involved and the uninvolved kidneys in the same patient is often striking. Urinary frequency or burning may or may not be marked. Anorexia is common and frequently the patient feels nauseated and sometimes vomits. There is a tendency to adynamic ileus, and the abdomen is often greatly distended with gas. The urine is apt to be scanty and concentrated, and urinalysis shows many pus cells. Gram stain of the urinary sediment and culture will show bacteria. The kidney function tends to be diminished temporarily. Unless some complicating factor is found (for example, a stone obstructing a ureter), neither plain x-rays or intravenous urography shows anything abnormal except reduction in kidney function. The diagnosis of acute pyelonephritis is made on the basis of the above signs and symptoms—malaise and sudden fever, possibly ushered in with a chill, anorexia or nausea, renal pain and tenderness, leukocytosis, pus and bacteria in the urine, although frequency or burning may or may not be marked.

Treatment. Since the kidney tubules are clogged with leukocytes and inflammatory exudate, these should be flushed out by maintaining a *considerable* intake of fluid by mouth, or, if the patient is nauseated or cannot take enough by mouth, by intravenous administration. In this early acute stage 3000 cc. of fluid per 24 hours should be taken by mouth or, if this is impossible, by the intravenous route unless the patient's circulation will *not stand it,* in which case hypodermoclysis may be resorted to. Since the embarrassed renal function tends to cause systemic acidosis, the carbon dioxide content of the blood should be esti-

or *Bacillus pyocyaneus (Pseudomonas aeruginosa)*. Cocci in clusters are probably staphylococci, whereas cocci in chains are streptococci. These observations can be used to guide therapy at the start—subject to confirmation by culture later.

SPECIFIC TYPES OF BACTERIAL INFECTION

At this time the bacteria, with the exception of the tubercle bacillus and the gonococcus, commonly producing infections of the urinary tract will be listed, the clinicopathologic characteristics of each type described, and the treatment most

TABLE I

BACTERIA COMMONLY PRODUCING INFECTIONS OF THE URINARY TRACT

Bacilli (All gram-negative)

"Enteric" type — colon-aerogenes-proteus group
- *Escherichia coli (Bacillus coli)*
- *Aerobacter aerogenes (Bacterium lactis aerogenes)*
- *Bacillus proteus*

Bacillus pyocyaneus (Pseudomonas aeruginosa)
Friedlander's bacillus (*Klebsiella pneumoniae* or *Bacillus mucosus capsulatus*)
Hemophilus influenzae (Pfeiffer's bacillus)
Bacillus faecalis alcaligenes
Paratyphoid or salmonella group

Cocci (All gram-positive)

Staphylococcus *(Staphylococcus aureus)*
(Staphylococcus albus)
Streptococci (mostly from Lancefield's Group D — Enterococci)
(usually aerobic, rarely anaerobic)
- Streptococci mostly of enteric origin
- *Streptococcus faecalis* (beta hemolytic and gamma nonhemolytic varieties)
- Enterococci
- *Alpha Streptococcus viridans*

Pleuropneumonia Organisms ("L" Bacillus)

efficacious for each will be given. It will be seen from the list that the common invaders of the urinary tract are either gram-negative bacilli or gram-positive cocci Every one of the species of bacteria listed has different strains within its species, each of which may differ in susceptibility to various drugs and antibiotics. Also during the course of treatment, the susceptibility of a strain may change and its resistance to the antibiotic may increase markedly. Simultaneous infections with more than one organism are unfortunately common. These are much more resistant to therapy and more difficult to treat than "pure" infections with only one organism, as will be brought out later

ACUTE PYELONEPHRITIS *(COLON BACILLUS)*

Let us now take up particular types of infection, first considering the commonest kidney infection—acute pyelonephritis, which is usually due to bacilli of the colon group. All writers are united in finding that the colon bacillus is the commonest organism found infecting the urinary tract, different observers giving the incidence from 60 to 80 per cent of all infections. Formerly this was called

acute pyelitis, but since the term "pyelitis" indicates inflammation limited to the kidney pelvis, and since this limitation of infection probably never occurs, as it has been found that the parenchyma of the kidney is invariably also involved, this condition is now thought of and referred to as acute pyelonephritis. As already stated, this may be blood-borne from an acute infection anywhere in the body, or may "ascend" from an infected bladder, often one that has recently been operated upon. Also it may follow cystoscopic ureteral catheterization or instrumentation.

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Symptoms, Signs, and Diagnosis. Clinically acute pyelonephritis starts with malaise and a sudden high fever, and may be ushered in with a chill. There is moderate leukocytosis. There is pain in the affected kidney, and tenderness and spasm to deep pressure in the corresponding costovertebral angle or to the "Murphy punch" in this region. This latter is a most reliable test of inflammation in and about the kidney, and consists of striking the costovertebral angle a light blow with the heel of the clenched fist when the patient is in the sitting or standing position. If there is inflammation present, the jarring of the blow causes the patient to wince from pain in the kidney, whereas if there is no inflammation the light blow causes no discomfort. The difference in this respect between the involved and the uninvolved kidneys in the same patient is often striking. Urinary frequency or burning may or may not be marked. Anorexia is common and frequently the patient feels nauseated and sometimes vomits. There is a tendency to adynamic ileus, and the abdomen is often greatly distended with gas. The urine is apt to be scanty and concentrated, and urinalysis shows many pus cells. Gram stain of the urinary sediment and culture will show bacteria. The kidney function tends to be diminished temporarily. Unless some complicating factor is found (for example, a stone obstructing a ureter), neither plain x-rays or intravenous urography shows anything abnormal except reduction in kidney function. The diagnosis of acute pyelonephritis is made on the basis of the above signs and symptoms—malaise and sudden fever, possibly ushered in with a chill, anorexia or nausea, renal pain and tenderness, leukocytosis, pus and bacteria in the urine, although frequency or burning may or may not be marked.

Treatment. Since the kidney tubules are clogged with leukocytes and inflammatory exudate, these should be flushed out by maintaining a considerable intake of fluid by mouth, or, if the patient is nauseated or cannot take enough by mouth, by intravenous administration. In this early acute stage 3000 cc. of fluid per 24 hours should be taken by mouth or, if this is impossible, by the intravenous route unless the patient's circulation will not stand it, in which case hypodermoclysis may be resorted to. Since the embarrassed renal function tends to cause systemic acidosis, the carbon dioxide content of the blood should be esti-

mated. The normal value for this is 26 to 28 milliequivalents per liter, and any value below 20 to 22 milliequivalents indicates acidosis If acidosis exists, it is combated by giving by mouth four times per day an alkali such as soda bicarbonate, 0 6 gm (10 grains), or as one teaspoonful 50 per cent solution of sodium citrate, until the acidosis has been corrected. In the patient too sick to take alkali by mouth, sodium racemic lactate may be given intravenously to combat acidosis Sodium racemic lactate is supplied in the form of an 11 per cent solution which is too concentrated for injection until it has been diluted by adding at least five times its volume of sterile distilled water. Ordinarily it is simplest to administer by adding it to a venoclysis In severe acidosis 5 to 10 cc. of the concentrated solution, properly diluted, is administered per kilogram of body weight.

In the very sick patient, the laboratory is an almost indispensable aid to the proper therapy For instance, frequent estimations of the CO_2 content of the blood give a guide as to whether active alkalinization by mouth or intravenously is necessary If the patient is vomiting, the fluid intake will have to be maintained by clysis, usually venoclysis Ordinarily 5 per cent dextrose in distilled water is administered. The blood chlorides should be followed carefully in the vomiting patient, because chlorides are being lost in the vomitus, and if the blood chloride level became abnormally low (normal level, 100 to 106 milliequivalents per liter), it is indicated to make up this deficiency by the administration of the 5 per cent dextrose in normal saline (sodium chloride), instead of in distilled water. The knowledge of the level of the nonprotein nitrogen of the blood (normal 15 to 35 milligrams per 100 cc.) or the blood urea nitrogen (normal 10 to 28 milligrams per 100 cc) is important as an indication of the effectiveness of total renal function, and also as an indication as to whether the patient is improving or is becoming uremic. The hemoglobin should be followed carefully, as patients with severe infections and high fevers tend to become anemic rapidly Not only is it detrimental in general for a patient to become anemic, but anemia also depresses renal function Anemia may be corrected rapidly by transfusions of whole blood, and rather slowly by the oral administration of iron in the form of ferrous sulfate 4 grains (0 25 gm) t.i d. A low serum protein may be found in association with anemia and in states of malnutrition or chronic draining wounds, and may be accompanied by edema and depression of bodily stamina It may be remedied by the administration of preferably whole blood but by plasma if the former is not available. A high protein diet will correct it slowly The normal total protein is 6 5 to 8 gm per 100 cc. In the case of high prolonged fever, blood culture may reveal a septicemia, which must be combated by the appropriate antibiotic or drug Thus in the very sick patient it is most important to follow the working of these physiologic processes of the body in order to take any remedial action indicated

Even before the advent of modern antibacterial drugs almost all cases of acute pyelonephritis without complicating factors (e g, obstruction by stone, hydronephrosis, etc.) soon got over the acute stage and became much better clinically, with no other treatment than forced fluids. However, now that efficient antibacterial agents are available, their judicious use shortens the

course and hastens the cure, but they should not be used indiscriminately and "poured on" thoughtlessly as a general antibacterial "tidal wave" to overwhelm any and all infections, because there are certain important considerations to be observed when they are employed.

In the first place, most cases of acute pyelonephritis are due to bacteria of the colon bacillus group, and since these and all the other gram-negative bacilli in the urinary tract are resistant to penicillin, the administration of penicillin is of little use in the many cases of pyelonephritis due to the colon bacillus or to other gram-negative bacilli. However, streptomycin is usually quite effective against organisms of the colon bacillus group. Nevertheless it has been found that bacteria which are not quickly overwhelmed by streptomycin rapidly develop a tremendous and permanent resistance to it, making its further administration useless. Therefore, since acute infections are most likely to occur in those patients with stasis, stone, etc., and since it is just such complicating factors as these which might prevent complete eradication of the infection by streptomycin, and thus bring about resistance to it, it seems wisest not to use streptomycin routinely at the outset, unless such complications have been ruled out—and these patients are often too sick to make a complete urologic examination desirable before treatment is started. However, if the urine culture showed presumably (or actually proved) susceptible bacteria, or even if a stain showed gram-negative bacilli, and there appeared to be a serious threat to life, so that it was imperative to use any and all means available, naturally streptomycin should not be withheld on the chance that some complicating factor would interfere with cure. An example of this is a severe case of pyelitis of pregnancy, where the dilated ureters and kidney pelves may interfere with eradication of the infection, but where every effort must be made on behalf of the mother and child

Mandelic acid therapy is exceedingly efficacious against colon bacilli, but since this requires limitation of fluids and extreme acidification of the urine—both of which must be avoided in acute pyelonephritis—it should not be used in the acute stage. Thus there are certain contraindications to the unconsidered routine use of penicillin, streptomycin, or mandelic acid in the usual case of acute pyelonephritis.

Sulfadiazine Therapy: In order to start some reasonably effective drug therapy as soon as possible in a sick patient with acute pyelonephritis, it is desirable to use some drug which is efficacious against most bacteria and as free as possible from undesirable effects. In this situation, the use of sulfadiazine, provided certain precautions are observed, is favored by the writer. The first precaution is to be sure that the sulfadiazine is not administered until there is a good urinary output at the rate of 2000 cc. per 24 hours, and the second measure to take is to alkalinize the urine Both of these have already been referred to, and are to be done routinely in acute pyelonephritis. Sulfadiazine is quite efficacious against the colon bacillus group, and reasonably so against staphylococci, and therefore can be started at once, regardless of which organism is causing the infection, and without waiting for examination of the urine for bacteria or for culture results. The author prefers sulfadiazine to the other sulfa drugs for reasons which will be discussed later. Frequently the infection

is thus cured by sulfadiazine, and the administration of an antibiotic such as streptomycin never becomes necessary. When sulfadiazine was first used, trouble was sometimes had from the plugging of ureters or kidney pelves with crystals of acetylsulfadiazine, or, rarely, with plugging of the kidney tubules with these crystals, or with the development of a toxic nephritis. It was found that these occurrences could be prevented by a liberal fluid intake and output, and by alkalinization of the urine, therefore, these two things should always be achieved without fail before and during the administration of sulfadiazine The urine is made alkaline by taking orally such alkalies as fruit juices, soda bicarbonate, or sodium citrate, or by the intravenous administration of sodium racemic lactate (as already described). The reaction of the urine should be tested regularly four times a day, and the pH values kept on a chart "Nitrazine" paper is convenient for this. The urine should always be maintained at a pH not lower than pH 6 0 to 6 5 and preferably 7 0 or 7.5. The author uses and recommends 1 gm of sulfadiazine orally four times per day. If the patient is too nauseated for oral administration, 2 gm of sodium sulfadiazine should be given intravenously every 12 hours. When giving only 4 gm. of sulfadiazine per day orally accompanied by forced fluids and alkalies, it usually is not necessary to follow the level of the sulfadiazine in the blood, as it does not get dangerously high. The intravenous administration of 4 gm of sodium sulfadiazine per day on account of inability to take medication by mouth, should be accompanied by plenty of intravenous fluids and sodium racemic lactate to make the urine alkaline, as already described In case this intravenous medication has to be maintained for more than 72 hours, it would be well to check the blood level of sulfadiazine, which should be 8 to 15 mg. per 100 cc blood However, in most cases the patient can take the drug by mouth within 72 hours When treating acute pyelonephritis, and especially when using sulfadiazine, the amount of the urinary output must be followed carefully At the start of therapy the output is scanty and the urine concentrated. As a result of the fluids administered the output of urine should rise rapidly and the urine become more dilute If the output does not increase within half a day and the urine remains concentrated, it is usually a sign that the fluid intake is insufficient and must be increased Also it is an indication to discontinue the sulfadiazine until the output is satisfactory and the urine more dilute.

The usual case of acute pyelonephritis begins to react favorably to the proper treatment at the end of 24 hours Therefore if after two to three days of adequate treatment (with increased fluid intake and output, alkalinization and sulfadiazine), the fever is still up and the patient is not much improved clinically, some complication, such as a stone blocking the kidney outlet or ureter should be suspected In this case urologic investigation must be carried out with excretion or retrograde pyelography and cystoscopy as indicated If any complicating factor is revealed, the acute infection may not abate much and certainly cannot be cured—until this complication has been eliminated

Within two or three days after treatment has been started, there will have been time to get the results of the urine culture and to identify exactly the bacteria causing the infection This is most important as a guide to the proper

treatment, because, as has been already mentioned, the effectiveness of drugs and antibiotics varies considerably according to the organisms against which they are being used. In the pyelonephritis under discussion, let it be assumed that the causative bacterium is the colon bacillus, which actually is the organism most commonly found clinically. The treatment of infections due to organisms other than the colon bacillus will be taken up in detail elsewhere.

When the acute phase of pyelonephritis is over, the fever and pain have abated, and the patient feels better, it is a grave mistake to take it for granted that the whole infection has necessarily gone, as in the case of an acute upper respiratory infection which has come to an end. Unfortunately the infection often tends to persist in a chronic form until, or unless, eradicated actively, especially if any perpetuating factor be present. Thus it may smoulder on in a slow, mild, insidious course—sometimes with occasional acute exacerbations—to become chronic incurable pyelonephritis which, if bilateral, eventually leads to chronic renal insufficiency and uremia. Therefore, since a complete bacteriologic cure is so important for the future, the same regimen of 4 gm. of sulfadiazine per day with alkalinization should be continued for one week after the temperature has become normal, and then half the dose of sulfadiazine for another week. In most uncomplicated cases, this will eliminate any residual infection which may remain after the acute stage has subsided. However, if the urinalysis does not become normal or the culture negative after this, the possibility of some complicating factor (e.g., stone or stasis) interfering with cure must be recognized and urologic studies undertaken. Unless the patient is unusually subject to allergic manifestations (in which case retrograde pyelograms may be preferable), intravenous urography—which will reveal obvious major pathology—is the study to be carried out first, as it is the simplest procedure and easiest for the patient. However, if intravenous urography leaves one in doubt—as it sometimes does—further urologic investigations should be carried out, such as cystoscopy, retrograde pyelography, determinations of residual urine and stasis, etc. It is the duty of the physician to follow and treat any case of acute pyelonephritis until a permanent bacteriologic cure has been obtained, seeking out and eradicating any factors which may tend to perpetuate the infection in order to forestall the development of incurable chronic pyelonephritis.

Chronic Pyelonephritis

Chronic pyelonephritis, once it becomes firmly established, usually cannot be cured nor its course halted. It may be unilateral, but frequently is bilateral and in such cases progresses gradually but steadily to death from chronic renal insufficiency and uremia. Clinically its course tends to be mild and insidious, punctuated with occasional periods of malaise and some fever. Urinary symptoms are frequently minimal, but the urine contains pus and bacteria In the terminal stages, as uremia deepens, anorexia, secondary anemia, and cachexia occur. Hypertension may or may not be present. Pathologically there is little frank suppuration, although there may be small abscesses in the parenchyma. The process is characteristically patchy in distribution, the chronic infection extending here and there in the kidney, with destruction of renal tissue, followed later by

healing, fibrosis, and contraction. There are scars in the cortex with a loss of both glomeruli and tubules, and the tubules which remain may contain colloid or hyaline casts. There is an increase of interstitial connective tissue which is infiltrated with lymphocytes and some leukocytes. The arteries show fibrous thickening of the wall with narrowing of the lumen The wall and the mucous membrane of the pelvis are thickened and chronically inflamed and the calices are dilated and blunted

CHRONIC PYELONEPHRITIS AND ARTERIAL HYPERTENSION

In 1934 Goldblatt and his co-workers described the experimental production of persistent arterial hypertension in dogs by causing ischemia of one kidney through partial constriction of the renal artery by means of a special clamp. This memorable work, confirmed by others and later extended to monkeys, directed attention to unilateral kidney disease as a possible cause of hypertension in man When unilateral chronic pyelonephritis was found in association with high blood pressure, it was thought that this hypertension was a result of the renal ischemia caused by the fibrosis of the parenchyma and of the arteries with narrowing of their lumina For this reason, since 1938 considerable numbers of patients with high blood pressure and unilateral chronic pyelonephritis have been subjected to nephrectomy of the diseased kidney Although the hypertension has been thereby remedied in a few of these cases, unfortunately in most cases it has not been influenced. Why one person with an ischemic kidney of chronic pyelonephritis should have hypertension, while another with exactly the same type of kidney does not have hypertension, is still an unanswered question. Another unanswered question is why should the hypertension of one person with unilateral chronic pyelonephritis be favorably affected by nephrectomy, while removal of a similar kidney does not change the hypertension of another? It has been observed that nephrectomy seldom benefits persons more than 45 years old or those in whom the hypertension has been known to be present for more than a relatively short time. Apparently after that, irreversible sclerotic changes have occurred in the arterioles of the body, and the removal of the diseased kidney cannot affect these changes or have a beneficial effect on the hypertension at that late date, even though that kidney may have been the original cause of the hypertension Homer Smith published in 1948 a most complete review of the whole subject of the relation of unilateral renal disease, including pyelonephritis, to hypertension, and of the results obtained by nephrectomy Of 242 nephrectomies for hypertension reported in the literature – and doubtless many more were performed but were not reported, possibly on account of unsuccessful results – Smith found only 47 "cures" where the blood pressure had been lowered to or below 140/90 for at least one year More than two-thirds of these successful cases were 39 years or less in age In nearly half (47 per cent) of these "cures" the renal lesion was pyelonephritis. Thus it can be seen that chronic pyelonephritis is an extremely dangerous disease, as it may lead to eventual kidney insufficiency, uremia, and death, and in some cases also to arterial hypertension and its sequelae *Therefore, in every case of acute urinary infection it is the serious* responsibility of the physician to eradicate it completely so as not to leave any smouldering residual infection which might develop into incurable chronic

pyelonephritis. It is uncured cases which pursue a slow insidious course — with occasional acute exacerbations — and produce the pathologic picture of a combination of healed pyelonephritis and acute pyelonephritis which, Weiss and Parker believe, not infrequently, leads to arterial hypertension.

TREATMENT OF PYELONEPHRITIS

Mandelic Acid Therapy. To return to the treatment of pyelonephritis: In any case where conditions which might interfere with bacteriologic cure, such as stasis or stone, etc., have been ruled out or eliminated, and yet residual infection does not yield to the administration of sulfadiazine, employment of a different drug is indicated. Continuing to assume that the colon bacillus is the infecting organism in the case under discussion, mandelic acid or streptomycin therapy may well be used, as both of these agents are very effective against this organism. That being the case, which of the two should be used, and why? Undoubtedly streptomycin is more powerful and has succeeded in cases where mandelic acid has failed. However, although streptomycin has to be prepared in a sterile manner, administered intramuscularly under aseptic conditions every 12 hours, it is not always free of toxic effects, and is more expensive than mandelic acid which is taken orally four times per day and seldom has toxic effects. Since all this makes the administration of streptomycin a more complicated and extensive procedure, and since mandelic acid is effective in most colon bacillus infections, it seems well to try this first, holding streptomycin in reserve, especially if the patient is not already in a hospital.

In order to have mandelic acid therapy working at its maximum effectiveness, the urine must be acid — the more acid the urine, the more effective the therapy. The pH should be maintained at least as low as pH 5.5 and preferably lower — pH 5.0 to 4.5 or even 4.0 Except in the case of urea-splitting infections, with either one or more than one organism (about which is more later), this acidification may be obtained by the administration of 10 grains (0.6 gm.) of acid sodium phosphate or 7½ grains (0.5 gm.) of ammonium chloride (preferably the enteric-coated tablet) four times per day with each dose of the mandelic acid. This latter is commonly supplied as a syrup in the form of its ammonium salt, ammonium mandelate, the ammonium radicle being added to produce an acid urine. The dosage is calculated to supply a total of 12 gm. of mandelic acid per day, divided into four doses each of 3 gm., usually taken with or after each of the three meals and again at bed time. Some patients object strenuously to the rather evil taste of this syrup, and the writer has found that it is best taken "straight" and then "chased" with water or some other beverage — this being done during or immediately after a meal, and at bed time after a little food. Fluids are limited to 1200 to 1500 cc. (40 to 50 oz.) per day in order to have the excreted drug present in as high a concentration as possible in the urine. As previously noted, in the acute febrile stage of a pyelonephritis limitation of fluids and acidification by means of drugs are contraindicated, so that mandelic acid therapy is not suitable until that acute stage has subsided This drug is so potent against colon bacilli and other gram-negative bacilli that great improvement may be expected within a few days, if the urine can be kept acid. By the same token, if improvement is not noted by the end of five to seven days, it can be assumed

that some unsuspected complicating factor is standing in the way of a cure. The usual length of a course of mandelic therapy is 10 to 14 days. Although the infection is suppressed and presumably extinguished by the first few days of therapy, it has been found that supposed cures are more apt to be permanent, without any exacerbation or recurrence of the infection, if the therapy is continued for another week or so. Mandelic acid is somewhat irritating to the kidneys, and in elderly patients with poor renal function and an elevated nonprotein nitrogen it may further depress renal function and cause more retention of nitrogenous products, and, therefore, in such patients it should be given with caution if at all. However, if renal function is not too abnormal no danger is to be feared No toxic allergic sensitivity to mandelic acid has been reported In addition to being effective against the colon bacillus, and also against other related gram-negative bacilli if the urine can be kept acid, mandelic acid is also quite effective against one of the organisms most resistant to drug therapy, the *Streptococcus faecalis,* about which more will be said later.

Bacteriologic Proof of Cure Sometimes the administration of bactericidal drugs and antibiotics does not completely eradicate infecting bacteria, but merely suppresses their growth temporarily, so that, after the drug has been discontinued, they will gradually "come to life" and flourish again. Consequently, in order to be sure that an infection has been really and permanently cured, it is well to wait at least one week after the drug has been stopped before making the final culture to be sure of the cure Frequently a culture taken just as the course of drug therapy is being finished will show no growth, but if the bacteria have not been truly eradicated, they will gradually grow again, and will give a positive culture after a week or so

Streptomycin Therapy If the subsided acute pyelonephritis of the gram-negative colon bacillus type has responded to neither sulfadiazine nor mandelic acid — and always provided that any factor which might stand in the way of a cure, such as stasis, etc, has been eliminated — therapy with streptomycin or aureomycin is indicated. Penicillin is ineffective against this type of organism, while streptomycin is probably the most powerful and effective agent available against colon bacilli and allied gram-negative bacilli Before going into details, one of the most important facts in regard to streptomycin which may affect the success of therapy must be strongly stressed This important consideration is the tremendous tendency of bacteria — unless overwhelmed early — to acquire rapidly permanent high resistance to streptomycin which makes its further administration absolutely useless. Finland and his associates have shown that in a matter of 12 to 24 hours the resistance of certain organisms to streptomycin may increase so greatly that further treatment is futile. The lesson from this is that haphazard streptomycin therapy is not only apt to fail but, worse still, may produce a permanent resistance to streptomycin on the part of the bacteria so treated, that may destroy the possibility of ever using it with success against those bacteria. Therefore, the patient must be prepared, "the stage set" and then the drug given in dosage large enough to overwhelm the bacteria rapidly and completely.

In addition to colon bacilli, other related gram-negative bacilli such as *Aerobactor aerogenes, Bacillus proteus, Klebsiella pneumonia* (Friedlander's bacillus), and *Hemophilus influenzae* (Pfeiffer's bacillus) are, as a rule, sensitive to strep-

tomycin, but *Bacillus pyocyaneus (Pseudomonas aeruginosa)* is not especially sensitive to that agent. However, marked differences in sensitivity to streptomycin have been observed in different strains of the same bacterial species, so that, if possible, before starting treatment in any given case the *in vitro* sensitivity to streptomycin of the particular strain present in that case should be determined. Hewitt has shown that, in individuals with reasonably good renal function, if the fluid intake is limited to 2500 cc. per day, 2 gm. of streptomycin per 24 hours, administered intramuscularly, will give a level in the urine of 250 micrograms of streptomycin per cubic centimeter of urine. If it is found that the bacteria are resistant to a higher level of the drug than can be obtained in the urine, the prospects for success with streptomycin treatment are poor. Admittedly sensitivity tests require the services of a trained bacteriologist and a good laboratory, advantages which are not available to every physician. If the bacteria are of a type presumably susceptible to streptomycin, but facilities for sensitivity tests are not available, and if it has been decided to give streptomycin, the chance of failure must be eliminated as far as possible by giving the drug in a large enough dose (4 gm. per day at the start) to be sure to maintain a concentration in the urine more than adequate to kill bacteria that are even moderately sensitive to streptomycin.

Finland and his co-workers, and Kane and Foley have brought out two very important facts, namely, that alkalinization of the urine makes the streptomycin much more effective (i e., in effect greatly increases the dose of streptomycin), and secondly that alkalinization of the urine tends to prevent bacteria from becoming resistant to streptomycin. Perhaps this latter is simply due to the fact that the larger effective dose of streptomycin overwhelms the bacteria before they have a chance to acquire resistance. At any rate alkalinization has made streptomycin therapy more effective and successful. Finland et al. consider alkalinization to be so important that they now prepare the patient with alkalies for 24 to 48 hours before giving streptomycin, in order to be sure that the urine is being maintained consistently alkaline. Probably the best way of achieving this is by giving 1 gm each of soda bicarbonate and potassium citrate four or five times during each 24 hours during the period that streptomycin is being administered Occasionally this dose of alkali has to be increased to get the desired urinary pH. One contraindication to this intensive alkalinization with soda bicarbonate is congestive heart failure with edema, where the intake of sodium must be kept low. The pH of each voiding should be determined and charted; it should not be lower than pH 7.0 and preferably pH 7.5 "Nitrazine" indicator paper is convenient for this.

Streptomycin is usually supplied in the form of its chloride or sulfate salt as a sterile dry powder, and for urinary tract infections should be given intramuscularly. Solutions for injection are prepared by dissolving each gram of streptomycin in 2 to 4 cc. of sterile pyrogen-free distilled water or physiologic saline solution. In view of the fact, already referred to, that organisms in the urine, unless rapidly overwhelmed by streptomycin, are apt to develop marked and permanent resistance to it, it is important to "hit hard" from the start. A dose of 4 gm per 24 hours will produce a level of the drug in the urine which is more than bactericidal for most organisms that are at all sensitive, especially if

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Streptomycin is usually supplied in the form of its chloride or sulfate salt as a sterile dry powder, and for urinary tract infections should be given intramuscularly. Solutions for injection are prepared by dissolving each gram of streptomycin in 2 to 4 cc. of sterile pyrogen-free distilled water or physiologic saline solution. In view of the fact, already referred to, that organisms in the urine, unless rapidly overwhelmed by streptomycin, are apt to develop marked and permanent resistance to it, it is important to "hit hard" from the start. A dose of 4 gm. per 24 hours will produce a level of the drug in the urine which is more than bactericidal for most organisms that are at all sensitive, especially if

preliminary alkalinization has been carried out. On starting the treatment, half the total dose to be given per 24 hours is administered intramuscularly and the second half is given 12 hours later, thus making two injections per 24 hours, 12 hours apart. This dose should be kept up for two days, and thereafter, if no severe toxic symptoms develop, half that dose is given for five days more. Toxic *reactions to streptomycin are not unusual, but are not usually severe. The most* serious of these are disturbances of the labyrinthine apparatus, consisting of vertigo (especially upon sudden motions as standing up), nystagmus, tinnitus, and sometimes impairment of hearing Such disturbances are not apt to occur when the drug is given for only a week, and may be expected to subside shortly after it is discontinued However in some cases where the drug has been given in full dosage for a prolonged period for tuberculosis, considerable and permanent impairment of hearing has resulted Other less important toxic symptoms are "drug fever," skin rashes of various types, general malaise with generalized aches and pains and arthralgia Pain and tenderness at the site of injection are not uncommon Streptomycin is slightly toxic to the kidneys, and there may be an increase of the nonprotein nitrogen of the blood during treatment In view of this, patients with abnormally high nonprotein nitrogen values or with poor renal function should be treated with great caution. Hyaline and granular casts may appear during treatment, but these disappear on withdrawal of the drug and there is no evidence that any permanent damage is produced.

If a cure is going to be effected, great improvement and often sterile cultures will be obtained in a few days Therefore, if no great improvement has occurred by the end of the week's course, it is probably useless to continue the drug longer, as it will be without effect, and also because after this time there is an increasing probability of toxic disturbances of the vestibular apparatus.

Dihydrostreptomycin Therapy. At first only one type of streptomycin was used However, in 1949 dihydrostreptomycin became available. This is derived from streptomycin by reduction with hydrogen, and is supplied as a powder in the form of dihydrostreptomycin hydrochloride From considerable clinical trial it now appears that it will soon supplant streptomycin because, while its antibacterial activity parallels that of streptomycin, it is markedly less neurotoxic, and vestibular and auditory dysfunction and damage are much less apt to occur. Thus 2 gm per day have been given for as long as four months without causing evidence of neurotoxicity This means that larger doses can be given for a longer period of time without producing nerve disturbances when using this rather *than streptomycin, which makes it a more powerful weapon than streptomycin.* This is of particular interest in the treatment of tuberculosis. It is prepared and administered intramuscularly in the same manner as streptomycin Although dihydrostreptomycin will undoubtedly soon supplant streptomycin, and the writer has had some satisfactory experience with this and is now using it in preference to streptomycin, nevertheless it is so new that the clinical experiences with it are slight in comparison to those with streptomycin whose effects are now well known. Therefore, therapy with streptomycin has been described, but with the thought in mind that dihydrostreptomycin, which is similar, may soon supplant it.

Aureomycin Preliminary clinical experiences with the antibiotic, aureomycin, indicate that it is effective against a wide variety of gram-negative and gram-

positive bacteria. It is administered orally in the dosage of 0.25 gm. every six hours for one week. It appears rapidly in the urine and is excreted continuously for two or three days after a single dose of 0.75 gm. Unlike streptomycin, there is little tendency for organisms to develop resistance to it, and, in a number of instances where one course was not successful in eradicating the bacteria, a second course, given after two weeks had elapsed, succeeded in curing the infection. Aureomycin also differs from streptomycin in that it is much more effective in an acid than in an alkaline medium, and when it is acting effectively the urine becomes highly acid and remains so throughout the treatment. Toxic effects are unimportant and infrequent. The commonest complaint is of frequent and bulky bowel movements, although not a true diarrhea. Nausea occasionally occurs. The drug does not cause anemia, agranulocytosis, evidence of liver damage, or of renal irritation as manifested by albuminuria, casts, or an increase in the nonprotein nitrogen of the blood. Also fever or rashes ascribable to the drug have not been observed. As regards infections of the urinary tract, early clinical experiences to date indicate that it is a valuable agent, and gives results comparable with, if not superior to, those obtained by streptomycin or the sulfa drugs It is very effective against infections due to the colon bacillus, *Aerobacter aerogenes,* and Friedlander's bacillus, but infections due to the *Bacillus proteus* and the *Bacillus pyocyaneus (Pseudomonas aeruginosa)* — both active urea-splitters — are extremely resistant to it Although the author does not know how successful it will be clinically against infections caused by the urinary streptococci and enterococci and by *Staphylococci aureus* and *albus,* it should be effective against these organisms *in vivo,* as they are all sensitive to it *in vitro.* Preliminary experiences indicate that this may prove to be the most potent and least toxic bactericidal agent for urinary tract infections yet discovered.

Gram-Negative Bacillary Infections Not Due to Colon Bacilli

In the preceding section acute and chronic pyelonephritis due to the gram-negative colon bacillus have been considered because this is the commonest organism found in such cases, and because renal infections due to most of the other gram-negative bacilli found in the urinary tract are, in general, somewhat similar in type to those produced by the colon bacillus, and their therapy is along similar lines. The commonest of these gram-negative bacillary invaders will now be described briefly.

Infections due to the Bacillus Proteus and the Bacillus Pyocyaneus (Pseudomonas Aeruginosa). Two invaders frequently found are the *Bacillus proteus* and the *Bacillus pyocyaneus (Pseudomonas aeruginosa).* Unfortunately these are in all probability artificial contaminants, as infections with either of them are almost never seen in any case that has not been catheterized, subjected to instrumentation, or operated upon. Furthermore, any patient who wears a nephrostomy or cystostomy tube or an inlying catheter for any length of time is almost certain to acquire an infection with one of these organisms. Clinically both of these organisms are active urea-splitters, and on account of the vicious circle of the mutually interdependent infection and lithiasis, which will be referred to later in the discussion of urea-splitting bacteria, it is usually extremely difficult and often impossible to eradicate infections due to these organisms, unless they have been

acquired recently and have not had time to become firmly entrenched. For practical purposes infections due to these organisms are not favorably influenced by penicillin or by the sulfa drugs, and it is usually impossible to get the urine sufficiently acid to use mandelic acid therapy.

"NU445": In the last two years a number of workers have tried "NU445," a sulfonamide derivative of low toxicity and great solubility, on *Bacillus proteus* infections. Although this drug seems to have more effect on proteus infections than any of the other sulfonamides, it still leaves much to be desired, as composite figures compiled from three recent articles show that only 50 per cent of the proteus infections upon which this drug was tried were cured. The dosage is 8 to 12 gm per day and alkalinization is not necessary.

This then leaves streptomycin as the most powerful agent against infections due to the proteus bacillus, and the only agent at all effective against *Bacillus pyocyaneus (Pseudomonas aeruginosa)* The results of streptomycin therapy of *Bacillus proteus* infections have been good when no complicating factors were present. Since the observations of some workers tend to show that the simultaneous administration of a sulfonamide with an antibiotic has increased the bactericidal effectiveness, it would seem reasonable to give 8 gm per day of "NU445" with the streptomycin when endeavoring to eradicate proteus bacillus infections After the course of streptomycin has been concluded, the author would suggest that "NU445" be continued for another two weeks at a dosage of 6 gm. per day

Even *in vitro* the *Bacillus pyocyaneus (Pseudomonas aeruginosa)* is only moderately sensitive to streptomycin, and *in vivo* it is not only somewhat resistant, but is apt to become more so rapidly When attempting to eradicate a pyocyaneus infection, the author would suggest the administration of 4 gm. per day of dihydrostreptomycin for at least one week

Infections Due to Other Gram-Negative Bacilli

Other gram-negative bacilli, producing infections similar in type to those of the colon bacillus, are the *Aerobacter aerogenes* and Friedlander's bacillus *(Klebsiella pneumoniae)*, both of which are quite susceptible to streptomycin, as already mentioned, although they are not easily influenced by other urinary antiseptics. The *Hemophilus influenzae* (Pfeiffer's bacillus) is a less common gram-negative bacillary invader which is quite sensitive to streptomycin, but since it is a urea-splitter it is frequently associated with lithiasis, and under these conditions its clinical eradication is apt to be difficult or even impossible, much as in the case of proteus and pyocyaneus infections Infections with paratyphoid or salmonella organisms occur occasionally, and aureomycin appears to be the best agent for use against them.

Urea-splitting Infections

At this point it seems well to discuss the subject of "urea-splitting" by bacteria — a phenomenon which prevents the cure of infections in many cases Many organisms break down or "split" the urea being excreted in the urine, thereby producing ammonia which makes the urine strongly alkaline at all times. In this alkaline urine — just as may be observed in the "alkaline tide" after a meal —

there tend to be constantly present many crystals of calcium phosphate, triple phosphate (ammonium magnesium phosphate), amorphous phosphate, and calcium carbonate. The constant presence of this abundance of crystals in conjunction with the infection of the kidney pelvis (or bladder) whose inflamed mucous membrane is giving rise to exudate and fibrin which the crystals can precipitate upon and coat, results in a great and well recognized tendency to calculus formation. Naturally these calculi have the same composition as the crystals of which they are formed, i.e., calcium phosphate, ammonium magnesium phosphate, and calcium carbonate. Once calculi have formed, it becomes impossible to eradicate permanently any infection as long as they are present, and also as long as the infection is present stones will continue to form — a vicious circle — and unhappily many such cases cannot be cured. In urea-splitting infections it is usually impossible to make the urine really acid by any means, which unfortunately means that "alkaline" crystals are constantly present in the urine, and that bactericidal therapy requiring acidification of the urine, such as mandelic acid therapy, cannot be used. The *Bacillus proteus* is the organism most notorious for urea-splitting, but it is followed closely in ability by the *Bacillus pyocyaneus*, some strains of colon bacilli, the staphylococci, all the streptococci belonging to Lancefield's Group D, and various other organisms found less commonly, including the *Hemophilus influenzae*. In fact, a surprisingly large number and variety of organisms may split urea. "Mixed" infections due to simultaneous infection with two or more different organisms (which will be discussed in the next paragraph) are also especially prone to urea-splitting, and may be impossible to eradicate.

"Mixed" Infections

A great many infections of the urinary tract are not "pure" infections with only one organism, but are "mixed" infections due to two — and sometimes more — organisms. In urinary tract infections of long standing, especially when associated with calculi or where the patient has been subjected to extensive instrumentation or to kidney or bladder operations, it is more usual to encounter "mixed" infections than infections with only one organism, which are commoner in recent acute infections. Every possible combination may occur, and no two organisms habitually "pair off" to the exclusion of others. The combination of a gram-negative bacillus with a gram-positive coccus is a very common one (e.g., *Bacillus coli* and *Staphylococcus albus*) as is the combination of two gram-negative bacilli (e.g., *Bacillus coli* and *Bacillus proteus*). Often one organism, e.g., *Bacillus proteus*, so predominates that on culture only the dominant one is found, it having overgrown all else on the culture plate In such cases, however, a Gram stain of the urinary sediment will reveal the presence of both, unless they are similar in appearance. This explains the phenomenon noted often after or during treatment when the bacteria seem to change, cultures indicating that the original [illegible]

[illegible] to get rid of the staphylococcus and that disappears from the culture, but the colon bacillus, being unaffected by penicillin, now starts to grow again and reappears in the culture. This phenom-

enon signifies that neither organism has been completely eradicated, but that the treatment has greatly depressed one organism while allowing the other to flourish On change of treatment, the depressed bacteria are now allowed to flourish, while the others are inhibited. Neither organism actually disappears or appears *de novo*. The writer has seen this repeatedly, and others have referred to it The lesson is obvious – the patient should be treated at the same time with drugs effective against both organisms or, better still, with one agent effective against both, if there is such an agent. Mixed infections have a great tendency to urea-splitting which, as already described, creates an alkaline urine full of phosphatic crystals and a marked tendency to the formation of calculi.

As a rule, mixed infections are much more difficult to cure than infections with only one organism, especially if the latter are recent. This may be partly due to the fact that many of the cases in which mixed infections are found are of long-standing chronic infection which tends to be recalcitrant to treatment Another factor is the frequent occurrence of urea-splitting and resultant calculi which defeat attempts at eradication of the infection Furthermore in mixed bacillary and coccal infections, the therapy used to eliminate one organism may not be effective against the other Therefore, taking the picture as a whole, the old motto "in union there is strength" seems to be true in the case of mixed infections since, for the reasons just mentioned, they are much harder to cure than recent infections with only one organism, and in many cases they present an insoluble problem and cannot be cured by any means now at our disposal In the writer's opinion, the best approach to the situation at the present time is first, to eliminate any factors which would prevent a cure, such as stone or stasis If surgery has had to be performed to accomplish this, sufficient time must be allowed for wounds to heal, and for granulation tissue inside the urinary tract to be covered with healthy mucous membrane Then comes the second stage of the attack, which consists of "hitting hard" with adequate dosage of bactericidal drugs and antibiotics Care must be taken to use therapy as effective as possible against all the bacteria present For instance, in a mixed colon bacillus and staphylococcus infection the use of penicillin alone might suppress the staphylococcal infection but would not seriously affect the colon bacillus Thus in the treatment of such an infection either a drug should be used which is effective against both organisms or else the appropriate drug for each organism should be given simultaneously The author's suggestion at the present time would be to "hit hard" with full doses of dihydrostreptomycin (2 gm intramuscularly every 12 hours) and penicillin (300,000 units aqueous suspension of crystalline penicillin G with procaine every 12 hours) for four days, followed by half the dose of dihydrostreptomycin (1 gm intramuscularly every 12 hours) and the same dose of penicillin for another four days This should then be followed by mandelic acid therapy for another two weeks Although this is admittedly "shot gun" therapy, it should have an inhibiting action on all bacteria which are present. In addition, during the intensive treatment with streptomycin and penicillin, the writer would suggest giving 4 gm per day of sulfadiazine or sulfasuxidine, as it has been shown that in certain persistent infections the combination of the sulfa drug with the antibiotic is more efficacious than the antibiotic alone.

At best, it is difficult to eradicate these mixed infections, and they must be treated vigorously if any chance of success is to be hoped for.

INFECTIONS DUE TO STREPTOCOCCI

At this point, the cocci (excluding gonococci) which infect the urinary tract will be considered. More than fifty years ago, Rosenbach gave the name *Streptococcus pyogenes* to an organism which he isolated from suppurative lesions. The name streptococcus or chain-coccus was given, as these bacteria characteristically grew in chains resembling strings of beads. Since then many other organisms have been discovered which are called streptococci because they grow in chains, but which may otherwise differ considerably from each other, both as to cultural characteristics and pathogenic properties. Thus cocci which form chains may be isolated from water, milk, dust, and the feces of man and animals. Although these are all streptococci, they may have little but their morphologic appearance in common with each other or with the pyogenic streptococci which are so important in causing infectious suppurative diseases. Generally some confusion exists in the classification of the streptococci infecting the urinary tract, owing chiefly to the fact that their biochemical behavior, including fermentation of carbohydrates, appearance, and activity on blood agar not only overlap, but may not always be constant characteristics. Foley, who has done much work on this problem, feels that this situation might be clarified by using serologic classification, which as yet is not commonly done. Although most virulent streptococci causing acute and serious infections in man in general are in Lancefield's Group A, in contradistinction the majority of the low-grade chronic streptococcal infections found in the urinary tract of man are caused by streptococci of Lancefield's Group D, the group of the enterococci This group contains both hemolytic (beta) and nonhemolytic (gamma) varieties of *Streptococcus faecalis*, frequently also called enterococci, as well as other streptococci, mostly of bowel origin. Strains of *Alpha Streptococcus viridans* may be found. These urinary tract streptococci produce a mild, low-grade but exceedingly persistent pyelonephritis, and show great resistance to drug therapy and also considerable ability, especially in combination with other organisms in "mixed" infections, to "split" the urea being excreted in the urine, thus producing ammonia, an alkaline urine, and calculi. The irresistible power of the process of urea splitting to produce calculi and thus to interfere with and prevent the cure of such urinary tract infections has already been commented upon. The ability of these Lancefield Group D streptococci to split urea is less than that of such active urea splitters as the *Bacillus proteus*, but it is nevertheless definite, especially in mixed infections. As regards treatment these various enterococcic streptococci may be considered together. The resistance of this group to drug therapy is marked. Sulfonamide drugs and streptomycin are ineffective Very large doses of penicillin or arsenical drugs have been known to be successful on some occasions and to fail on others. In some cases all types of therapy tried have failed. The therapy of choice is mandelic acid which is not only the most effective but the simplest to carry out. After the usual two weeks' course, as previously outlined, has been completed, the writer would then recommend three "mandelamine" tablets four times per day for another two

weeks. Should this fail, our choice would be for massive doses of aqueous suspension of crystalline penicillin G with procain (300,000 units intramuscularly every 12 hours for a week), accompanied by a simultaneous two weeks' course of mandelic acid therapy. Oxophenarsine hydrochloride ("mapharsen"), 0.04 to 0.06 gm. intravenously every four days for a total of six doses, would be the third choice. The usual precautions should be observed when using arsenical drugs. Perhaps the new antibiotic, aureomycin, may prove effective, but the writer has no information on this point.

Chronic Infections due to Staphylococci

Staphylococcal infections of the urinary tract are of two general types: (1) the acute metastatic infections of the renal parenchyma due to the *Staphylococcus aureus* in which the pelvis is usually not involved, such as the so-called carbuncle of the kidney, (2) the usually mild and chronic pyelonephritis due to either the *Staphylococcus aureus* or *albus*, which will be considered first.

In this latter type of pyelonephritis the infecting bacteria may come from foci in the teeth, tonsils, or elsewhere, as previously described, and produce a pyelonephritis which may be acute at its onset but which soon lapses into a mild low-grade but chronic condition, closely resembling that produced by the Lancefield Group D streptococci. A further similarity is that these staphylococci also split urea, especially in mixed infections, and to a somewhat greater extent than the streptococci, and that these infections are apt to be accompanied by renal stone formation Also in their chronic state they are rather resistant to drug therapy, although not so resistant as the streptococci Again streptomycin therapy is not indicated, but large doses of penicillin are effective in many cases although not in all. Failure may be attributed to the staphylococci acquiring abnormally great resistance to penicillin, which sometimes occurs, and which results in the usual dose being insufficient for eradication In some cases sulfadiazine is employed effectively, in others mandelic acid, while sometimes combined therapy with penicillin and mandelic acid is successful. Occasionally recourse to the arsenicals is successful. Preliminary indications are that aureomycin may be quite effective against staphylococci The multiplicity of agents used is an indication that no one drug is consistently successful against these mild but persistent infections In these cases of staphylococcal infection it is important to seek out and eradicate any foci of infection existing in the teeth, tonsils, etc., which may stand in the way of establishing a permanent cure.

Acute Focal Renal Infections due to Staphylococci

In contrast to the chronic low-grade staphylococcal pyelonephritis just described, there is another type of more violent staphylococcal renal infection — the acute metastatic hematogenous infection of the renal parenchyma, usually without involvement of the renal pelvis. The staphylococci are brought to the kidney by the blood stream from foci usually outside the urinary tract, such as furuncles or a carbuncle, acute otitis media or complication of osteomyelitis, an infected wound (paronychia) or skin lesion (dermatitis) or an acute upper respiratory infection (pharyngitis or tonsillitis). A history of several furuncles ("boils") is especially common When a group of staphylococci is carried by the

blood stream to a kidney the invading bacteria create a local area of inflammation and infection in the kidney parenchyma. However, if the infection is minimal it may be overcome by the powers of resistance of the local kidney tissues, and spontaneous healing will ensue. Undoubtedly this phenomenon occurs far oftener than is realized.

However, the staphylococci may be of such numbers or virulence as to gain a firm foothold in the kidney parenchyma. The bacteria lodge in the glomerular capillaries, and are attacked by polymorphonuclears with the formation of pus and small focal abscesses. Characteristically these abscesses do not communicate with the kidney pelvis, and pus is usually not present in the urine. (This involvement primarily of the glomeruli without involvement of the pelvis is in contradistinction to the pyelonephritis characteristically produced by the colon bacillus type of infection where the pelvis is involved and the tubular system tends to be attacked and there is much pus in the urine.) Nevertheless the staphylococci themselves somehow filter through into the pelvis, and may usually be found in the urine.

The most severe form of this type of infection is the so-called pyemic kidney which occurs in the terminal stage of acute staphylococcal septicemia and is usually seen at the necropsy table. The condition is usually bilateral, and both kidneys are riddled with multiple small staphylococcal abscesses.

In their mildest form these focal staphylococcal renal infections tend to heal themselves. However, if the diagnosis can be made, intensive penicillin therapy will help recovery, and may also prevent an early infection from progressing to clinical abscess formation, which is what happens when the infection is of such severity as to become established in the parenchyma.

If an abscess forms far out in the cortex of the kidney near the capsule, it may break out through this capsule and form an abscess in the perinephric space formed by Gerota's fascia and usually occupied by fat. It is now thought that hematogenous staphylococcal perinephric abscesses form in this way, rather than by deposition of bacteria in the perinephric fat by the blood stream Frequently by the time the perinephric abscess comes to operation it is found that the abscess in the renal cortex has healed.

If the staphylococci take root more deeply in the kidney parenchyma, infection and abscess formation occur deeper in the kidney. Sometimes this abscess formation becomes so extensive and honeycombed as it extends through the parenchyma that it has the appearance of a carbuncle of the skin and so is called a carbuncle of the kidney. This may or may not extend outside the kidney, to give rise also to a perinephric abscess, but in any case it is uncommon for such an infection to invade the pelvis, which accounts for the fact that pyuria usually is not present in such cases. Thus when a perinephric abscess exists, the possibility of a coexisting kidney lesion must be anticipated, although frequently none is found, the small causative abscess in the kidney cortex having healed as already stated

The [illegible] infection are fever, leukocytosis, pa[illegible] with a positive "Murphy punch" test, but often no pus in the urine, although staphylococci can almost always be cultured from the urine from the affected kidney or found on a Gram stain of

the urine sediment. In the early stages or less severe forms, the x-ray is not informative, although sometimes on intravenous urography there may be diminution of renal function However, in the more severe forms, as in renal carbuncle, pyelograms may reveal a good-sized, usually circular, pressure defect of the calices or pelvis, which may also be accompanied by obvious localized bulging of the adjacent part of the kidney. Sometimes the upper ureter is seen to be pressed upon or deflected medially by a soft tissue mass. Occasionally the pyelographic picture leads to the mistaken diagnosis of renal neoplasm. In addition, if a renal abscess or carbuncle is accompanied by perinephric abscess there will be the additional findings associated with that process which will now be described.

Perinephric Abscess (Staphylococcal)

The earliest signs and symptoms of perinephric inflammation are minimal, and frequently the clinical course of a perinephric abscess is so insidious and slow that the diagnosis is not made until the process is far advanced and the patient may have been suffering from chronic sepsis for a period of weeks or even months In this connection, the history of a series of furuncles, a carbuncle, an infected hand or foot, or an infection of the skin, in any person who is running a septic type of daily afternoon and evening fever, should bring to mind the possibility of perinephric abscess The usual perinephric abscess slowly increases in size, sooner or later giving rise to tenderness and spasm on the affected side, a positive "Murphy punch," and, late in the disease when the abscess is large, fullness and even bulging of the flank There is unwillingness and even inability to bend the spine laterally away from the affected side on account of pain In fact, the spine is frequently held in lateral flexion concave toward the side where the trouble is. This shows up quite strikingly in an x-ray Often the shadow of the lateral margin of the psoas muscle, which usually appears by x-ray as a sharp line just medial to the kidney shadow, is clouded or obliterated by the soft tissue mass Furthermore in all cases of perinephric inflammation the kidney is fixed by the inflammatory process so that it does not move and make the customary 1 to 2 inch excursion up and down on expiration and inspiration, or on shifting from the recumbent position to the erect one This is shown clearly by x-ray where the immobility of the kidney on the affected side is in contrast to the mobility of the normal kidney Occasionally, the abscess causes irritation of the psoas muscle, resulting in psoas contraction and flexion of the hip joint, suggesting disease of the hip or psoas abscess originating from bone disease. If renal carbuncle is also present there may also be x-ray findings suggestive of that condition which has already been described.

Treatment of Staphylococcal Focal Renal and Perinephric Infections. Since the two conditions are so closely related – and often associated with one another – the treatment of focal staphylococcal renal infection and of perinephric infection will be discussed together. The early stages of focal staphylococcal renal infection or of perinephric inflammation or cellulitis – before abscess formation has taken place – may be favorably affected by intensive penicillin therapy, although *after a frank abscess has formed either in the kidney or in the perinephric region,* penicillin probably cannot cure, and surgery is necessary. Therefore, in the early stages a thorough trial with penicillin is indicated on the chance that, if abscess

formation has not occurred, the inflammation may thus be cured and an abscess prevented. The therapy recommended for this is 300,000 units of aqueous suspension of crystalline penicillin G with procaine added to eliminate "stinging" at the site of injection, given intramuscularly once every 24 hours for one week. At the

TABLE 11

BACTERIA COMMONLY CAUSING URINARY INFECTIONS AND THE AGENTS EFFECTIVE AGAINST THESE

Organism	*Agents In Order of Their Effectiveness*
Bacillus coli	Aureomycin
	Streptomycin
	Dihydrostreptomycin
	Mandelic acid
	Sulfadiazine
	Sulfathalidine
	"Mandelamine"
	Sulfasuxidine (with streptomycin)
	Methenamine
Aerobacter aerogenes	Aureomycin
	Streptomycin
	Dihydrostreptomycin
	Sulfadiazine
	(Mandelic acid)
Bacillus proteus	Streptomycin or dihydrostreptomycin
	N.U. 445
	(Singly or together)
Bacillus pyocyaneus (*Pseudomonas aeruginosa*)	Streptomycin
	Dihydrostreptomycin
	Mandelic acid
Friedlander's bacillus (*Klebsiella pneumoniae*)	Streptomycin
	Dihydrostreptomycin
	Aureomycin
Hemophilus influenzae (Pfeiffer's bacillus)	Streptomycin
	Dihydrostreptomycin
Staphylococcus aureus	Penicillin
Staphylococcus albus	Aureomycin
	Sulfadiazine
	Mandelic acid
	"Mapharsen"
	(Streptomycin)
Streptococci	Mandelic acid
Enterococci	Penicillin
	Aureomycin
	"Mapharsen"
Pleuropneumonia organisms ("L" bacillus)	Streptomycin
	Dihydrostreptomycin
Paratyphoid salmonella group	Aureomycin
	(Streptomycin)

end of that time any inflammation amenable to penicillin therapy should be cured, and if signs of infection still persist, it indicates that penicillin treatment alone cannot be successful in that case, and that abscess formation has probably taken place, and surgery must be resorted to. In such an eventuality, it has often been found that, while the penicillin was not able to cure the abscess, the bacterial activity in the abscess was so depressed that it took days or even weeks for the activity in the abscess to exacerbate and declare itself. If this phenomenon

TABLE III

ANTIBACTERIAL AGENTS AND BACTERIA AGAINST WHICH THEY ARE EFFECTIVE

Agent	*Effective Against*	*Administration*	*Optimum Reaction of Urine*
Sulfadiazine	*Bacillus coli* *Aerobacter aerogenes* *(Staphylococcus aureus)* *(Staphylococcus albus)*	1 gm (15 gr) by mouth 4 times per day Urine to be kept alkaline with 0 6–1 0 gm (10–15 gr) soda bicarbonate 4 times per day or with 1 teaspoonful 50 per cent solution sodium citrate 4 times per day Urinary pH checked 3 times per day *Must have good fluid intake (3000 cc per 24 hours), and output (2000 cc per 24 hours)* After 1 week, reduce dose of drug to 0 5 gm (7 5 gr) 4 times per day for another week Penicillin sometimes administered simultaneously for staphylococcal infections	Alkaline—important
Penicillin	*Staphylococcus aureus* *Staphylococcus albus* Streptococci-Enterococci (Not effective against bacilli)	300,000 units of aqueous suspension of crystalline penicillin G with procaine (no oil or wax) given intramuscularly every 12 hours for 1 week (Sulfadiazine sometimes administered simultaneously for staphylococcal infections)	Acid
Streptomycin	*Bacillus coli* *Aerobacter aerogenes* *Bacillus proteus* Friedlander's bacillus *(Klebsiella pneumoniae)* *Hemophilus influenzae* (Pfeiffer's bacillus) Pleuropneumonia organisms ("L" bacillus) *(Bacillus pyocyaneus)* *(Pseudomonas aeruginosa)* *([Staphylococcus aureus])* *([Staphylococcus albus])* (Not usually used against streptococci)	Before starting administration urine is made constantly alkaline with soda bicarbonate 0 6–1 0 gm (10–15 gr) 4 times per day or 50 per cent solution sodium citrate 1 teaspoonful 4 times per day Urinary pH checked often and charted Fluids somewhat limited 2 gm streptomycin given intramuscularly every 12 hours for total of 4 doses Thereafter 1 gm every 12 hours for 5 days more Discontinue if dizziness appears	Alkaline—important
Dihydrostreptomycin	Same bacteria as streptomycin	Administration details the same as for streptomycin, except that 2 gm are given intramuscularly every 12 hours for 1 week Not so apt to cause dizziness	Alkaline—important
Aureomycin	*Bacillus coli* *Aerobacter aerogenes* Friedlander's bacillus *(Klebsiella pneumoniae)* ?(Streptococci-Enterococci) ? *?(Staphylococcus aureus-albus)?* Paratyphoid-salmonella group	Urine first acidified with 0 5 gm (7½ gr) ammonium chloride (enteric-coated preferred) 4 times per day or 0 6 gm (10 gr) acid sodium phosphate 4 times per day *Urinary pH* should be checked several times per day and charted After 2 doses of acidifying drug aureomycin is given orally in the dosage of 0 25 gm every 6 hrs for 1 week Once aureomycin is started, may not need acidifying drugs as ammonium chloride or acid sodium phosphate, because aureomycin acidifies the urine	Acid—important

Mandelic Acid	*Bacillus coli* *Staphylococcus aureus* *Staphylococcus albus* Streptococci-Enterococci *Bacillus pyocyaneus* *(Pseudomonas aeruginosa)* *(Aerobacter aerogenes)*	Urine first acidified with 0 5 gm (7½ gr) ammonium chloride (enteric-coated preferred) 4 times per day, or 0 6 gm (10 gr.) acid sodium phosphate 4 times per day Give 2 doses before starting mandelic therapy Limit fluid intake moderately (*1200–1500 cc per 24 hrs*) Check pH of urine often and chart Author prefers syrup of ammonium mandelate and gives enough of this orally, according to its strength, to administer 3 gm of mandelic acid 4 times per day for 10 days Penicillin sometimes administered simultaneously for staphylococci and streptococci-enterococci	Acid—important
"Mandelamine" (methenamine mandelate)	*Bacillus coli* *Staphylococcus aureus* and *albus* Streptococci-Enterococci	Urine first acidified as for mandelic acid Then 3 tablets 'mandelamine' given orally 4 times per day for 2–4 weeks Fluids limited slightly Urinary pH to be checked 2 times per day	Acid—important
"Mapharsen" (oxophenarsine-hydrochloride)	Streptococci-Enterococci *Staphylococcus aureus* and *albus*	0 04–0 06 gm intravenously every day 4 days for a total of 6 doses	
Methenamine (Hexamethylenamine—"Urotropin")	*B coli* and other bacilli except active urea-splitters Cocci except active urea-splitters	Urine first acidified as when administering mandelic acid, and pH checked. Then 0 5—0 65 gm (7½-10 gr) of methenamine, dissolved in water, is given orally 4 times per day. Usually given for not less than 10 days and sometimes for weeks	Acid
Sulfathalidine	*Bacillus coli*	1–2 gm orally 4 times per day for 10 days	Unimportant
Sulfasuxidine (with Streptomycin)	*Bacillus coli*	1 gm. orally 4 times per day. After sulfasuxidine has been taken for a few days, and urine has also been made alkaline, Crowley and O'Connor give 0 5 gm streptomycin intramuscularly morning and night for 5 days only, but keep on with the sulfasuxidine for many weeks more. Reported to have given good results in chronic stubborn colon bacillus infections	Alkaline
"N U.445"	*Bacillus proteus*	2–3 gm. orally 4 times per day for at least 10 days.	Unimportant

occurs, it usually results in the necessary surgery having been postponed on account of the earlier apparent cure of the infection. This does the patient no physical harm, and the possibility of obtaining a cure by penicillin in early stages is deemed worth taking this chance. Thus, unless a case is seen in an early stage, treatment by penicillin alone is not successful, but it has proved to be a valuable adjunct to surgery where it is indicated in the dosage of 300,000 units of aqueous suspension of crystalline penicillin G with procaine injected intramuscularly twice daily.

In the past, the surgery indicated in cases of renal carbuncle was usually nephrectomy, since the process had involved the kidney so extensively that simple drainage of the carbuncle was apt to end in failure, as the entrenched infection continued to smoulder and burrow throughout the kidney, eventually destroying it and necessitating its removal. There were, of course, some exceptions to this where simple drainage was successful, and nowadays, by the use of intensive penicillin therapy in conjunction with surgical drainage, it should be possible to save more kidneys from destruction and eventual removal.

As regards the surgery of perinephric abscess, needless to say thorough drainage is required, and sometimes it may be necessary to explore the entire perinephric region in order to find a small abscess. As already mentioned, an abscess or carbuncle of the kidney may be present and should be looked for. As previously stated frequently the diagnosis of perinephric abscess is not made until it and any accompanying renal carbuncle have become extensive, and the patient has been suffering from chronic sepsis for a considerable time and has become debilitated. In such a cachectic patient, even though on drainage of the perinephric abscess the kidney is found to be so badly damaged by sepsis as to call for nephrectomy, if the condition is septic and poor, it may be the part of wisdom to be content with drainage only of the renal carbuncles, and to postpone the nephrectomy until such time as the patient's general condition has improved, meanwhile administering intensive penicillin therapy.

Necrotizing Renal Papillitis

An interesting and rare form of acute pyelonephritis, which has been described only fairly recently, and which as yet may not be generally recognized, is necrotizing renal papillitis. This is a type of acute pyelonephritis in which abscesses become confluent in the renal pyramids about two-thirds of the way from the tip of the papillae to the junction of the pyramids and the cortex. This abscess formation interferes with the blood supply of the pyramids, resulting in a complete infarct-like necrosis or gangrene of the terminal two-thirds of the pyramids which, of course, includes the papillae. In advanced lesions, portions of the papillae break off, and even the whole papilla may slough out. In most cases all pyramids of the affected kidney are involved, and usually but not always the process involves both kidneys. Varying amounts of the more usual type of acute pyelonephritis are always found in the cortex of these kidneys. It is felt that healing does not occur, as the chronic, healing or healed stage has never been recognized. As might be expected, this condition is almost always fatal, the only exception being the rare cases who have survived following the

removal of a kidney in which papillary necrosis was found, and whose survival has postulated that the remaining kidney was uninvolved.

Clinically an important feature is that this disease occurs largely in diabetics. It may also occur in non-diabetics but is quite rare. When it does occur in non-diabetics, it is apt to be a complication of infection secondary to urinary tract stasis due to prostatic obstruction in elderly men. In contrast, the diabetic group is somewhat younger and urinary tract obstruction is rare. In such an unusual and clear-cut lesion it might be expected that one particular specific organism would be found to be the causative agent. This, however, is not the case as various organisms have been found in these kidneys, as *Bacillus coli*, *Staphylococcus aureus*, hemolytic and non-hemolytic streptococci, *Bacillus proteus*, and *Klebsiella pneumoniae*. Mixed infections are not uncommon. The usual clinical course is an acute fulminating one, and the patient — usually a diabetic — enters the hospital seriously ill with the history of the sudden onset of symptoms suggestive of a severe generalized systemic infection with prostration, high spiking temperature, and rapid pulse. Invariably the urine shows pyuria and bacterial infection. The course is rapidly fatal, being characterized by oliguria or even anuria and rapidly progressing uremia which is the cause of death in most patients. Septicemia with positive blood cultures is often found, and some patients die of overwhelming infection.

There is a second type with a less acute but equally fatal clinical course, in which, after weeks or months of subacute pyelonephritis characterized by remissions and exacerbations, the patient's condition suddenly becomes much worse and deteriorates rapidly until death ensues in a few days in the same manner as in the acute fulminating cases. It is felt that this represents a condition of subacute pyelonephritis upon which necrotizing papillitis is suddenly superimposed

In the past, antemortem diagnosis has been rare, and it can be argued that, since the affected kidney or kidneys are doomed, arriving at the correct clinical diagnosis before death is of no practical importance. However, since it is a suddenly developing and rapidly progressing bacterial lesion which must be treated intensively and immediately with the proper antibacterial agents as well as with general supportive treatment, if there is to be any possible hope of cure, and unless one is to adopt a nonprogressive and defeatist attitude of complete resignation and pessimism as regards attempting to save the patient, an early diagnosis is all-important. In this connection, retrograde pyelography may demonstrate an irregular moth-eaten eroded appearance of the renal calices due to sloughing of the papillae. This appearance may be much like that of pyelograms in advanced renal tuberculosis. Knowledge of the existence of this condition is also important in view of the fact that the necrosis of the tips of the papillae which impairs the urinary drainage of the associated nephrons constitutes a contraindication to the use of the sulfa drugs, in view of their well-known tendency to precipitate out in the renal tubules if the flow of urine is not free. Thus, in addition to general systemic supportive measures as outlined in the treatment of acute pyelonephritis, the drug therapy indicated in this condition is either massive doses of streptomycin, if the organisms are colon bacilli or

related susceptible organisms, or massive doses of penicillin for susceptible bacteria as staphylococci, or if in doubt, or until cultures can be grown, or for a mixed bacillary and coccal infection very large doses of both streptomycin and penicillin. The condition is so lethal that everything possible must be tried

Necrotizing renal papillitis must be suspected in severe acute urinary tract *infections, particularly in diabetics but also in nondiabetics with urinary obstruction*, where the patient suddenly becomes seriously ill, there is oliguria, and the nonprotein nitrogen of the blood is rising rapidly.

ABACTERIAL PYURIA

So-called abacterial pyuria (also called amicrobic pyuria or acute exudative or hemorrhagic cystitis of undetermined etiology) is an uncommon disease whose etiology has not been determined. Most of the cases observed have been in young adult males, many of them soldiers. The first symptom is frequently an acute urethritis in which no gonococci or other organisms can be found on *smear or culture. Sexual exposure may have preceded this in some cases. After* the discharge, which is unaffected by sulfa drugs or penicillin therapy, has lasted from one to three weeks the patient develops an extremely severe cystitis with marked frequency, urgency, burning, and not only pyuria but also hematuria, sometimes profuse. The symptoms are so severe during this acute period that the patient may be confined to bed most of the time.

Cystoscopy at this time shows an intolerant bladder with an intensely inflamed and edematous mucosa, often with ulcerated hemorrhagic areas and a lot of fibrinous exudate The bladder becomes markedly contracted because of this inflammation, with a capacity of only an ounce or two In most but not all cases there is dilatation of the kidney pelves and calyces, and of the ureters down to the bladder It is possible that this dilatation may be due to involvement of the kidneys and ureters by this severe inflammation, but this seems unlikely as there is only low grade fever and no tenderness in the kidney regions or chills. The probable explanation of this dilatation is that it is caused by obstruction to the lower ureters by the contracted and inflamed bladder Further evidence in this direction is that the inflammatory edema in some cases is such that ureteral catheters cannot be passed up the ureters, and in other cases the urine obtained on ureteral catheterization is either free of pus or shows very little. The bladder picture of acute hemorrhagic cystitis combined with dilatation of the ureters and kidney pelves is often suggestive of tuberculosis, and nephrectomies have been performed with this mistaken diagnosis *The cystitis tends to run a protracted* course over months Along with the urethritis and cystitis, some patients develop polyarthritis of various joints, such as the knees or elbows, and a few develop conjunctivitis, iritis, or dermatitis. As has been previously stated, all cultures are negative including those for tubercle bacilli Sulfa drugs and penicillin are of no avail However, arsenicals (e.g., neoarsphenamine 0 3 gm. intravenously every three to five days for a total of five doses) seem to be rather specific and bring about marked improvement and eventually cure More recently streptomycin has been used with success. However, unless arsenicals or streptomycin are used the disease tends to run a protracted and incapacitating course of many months, and even after their administration cure is not always

rapid and dramatic. After recovery the capacity of the bladder increases and the dilatation of the ureters and kidney pelves regresses in the direction of normal.

The fact that the etiology of this disease is as yet undetermined has aroused much interest and speculation. Some believe it to be a virus disease. One group in Chile reports finding spirochetes by darkfield examination of the centrifuged sediment of the urine in 6 cases. They were of the opinion that these organisms were probably of the type belonging to the buccal flora. In their cases dental treatment was given as indicated and arsenicals were administered, and cures were obtained. The fact that arsenical drugs are so effective in this condition would support a spirochetal etiology.

Reiter's Syndrome

In 1916 Reiter reported the case of a young German officer who, following an acute gastro-intestinal upset, had acute nongonorrheal urethritis with intense cystitis, conjunctivitis, and polyarthritis. All routine cultures were negative, but Reiter thought that a spirochete in the blood stream was the etiologic agent and called the condition "spirochaetosis arthritica." Although others were unable to find the spirochete, this triad of nongonorrheal urethritis, conjunctivitis, and arthritis with negative cultures was recognized as a definite syndrome and named after Reiter, and at least 65 cases have been reported since then. There are sometimes dilatation of the upper urinary tract, resistant to sulfa drugs and penicillin, and a long incapacitating course before eventual recovery. Despite minor differences cases of Reiter's syndrome have, in general, so much in common with those of so-called abacterial pyuria (including dilatation of the upper urinary tract producing a picture suggestive of tuberculosis) that it seems not unlikely that they have a similar etiology.

Infections due to Pleuropneumonia Organisms ("L" bacillus)

Quite recently there have been reported cases of urethritis, prostatitis, or cystitis, sometimes accompanied by polyarthritis and conjunctivitis – thus fulfilling the requirements for Reiter's syndrome – in which the usual cultures have been negative, but in which special culture methods have shown organisms belonging to the pleuropneumonia group, apparently the etiologic factor in these cases. The organisms belonging to the pleuropneumonia group are peculiar in that they have properties common to viruses of being filtrable and invisible on the usual stained smear, but, unlike the viruses, can be cultivated in lifeless media, frequently requiring anaerobic conditions. Pleuropneumonia organisms were first cultivated in 1898 from cattle and were recognized as the cause of the disease, bovine pleuropneumonia. Strains of these organisms have also been found in other animals, as goats, rats, and sheep. Diseases in animals caused by these organisms tend to be chronic and involvement of joints is common. Organisms belonging to the pleuropneumonia group – the so-called L bacillus – were first cultivated from humans in 1937. All strains of these organisms are closely similar in their appearance, the growth of their colonies, and their staining and physical properties. The organisms cannot be found in the usual type of stained smear employed in bacteriology because they are so soft and fragile that

related susceptible organisms, or massive doses of penicillin for susceptible bacteria as staphylococci, or if in doubt, or until cultures can be grown, or for a mixed bacillary and coccal infection very large doses of both streptomycin and penicillin. The condition is so lethal that everything possible must be tried.

Necrotizing renal papillitis must be suspected in severe acute urinary tract infections, particularly in diabetics but also in nondiabetics with urinary obstruction, where the patient suddenly becomes seriously ill, there is oliguria, and the nonprotein nitrogen of the blood is rising rapidly.

Abacterial Pyuria

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Cystoscopy at this time shows an intolerant bladder with an intensely inflamed and edematous mucosa, often with ulcerated hemorrhagic areas and a lot of fibrinous exudate The bladder becomes markedly contracted because of this inflammation, with a capacity of only an ounce or two. In most but not all cases there is dilatation of the kidney pelves and calyces, and of the ureters down to the bladder. It is possible that this dilatation may be due to involvement of the kidneys and ureters by this severe inflammation, but this seems unlikely as there is only low grade fever and no tenderness in the kidney regions or chills The probable explanation of this dilatation is that it is caused by obstruction to the lower ureters by the contracted and inflamed bladder. Further evidence in this direction is that the inflammatory edema in some cases is such that ureteral catheters cannot be passed up the ureters, and in other cases the urine obtained on ureteral catheterization is either free of pus or shows very little. The bladder picture of acute hemorrhagic cystitis combined with dilatation of the ureters and kidney pelves is often suggestive of tuberculosis, and nephrectomies have been performed with this mistaken diagnosis The cystitis tends to run a protracted course over months. Along with the urethritis and cystitis, some patients develop polyarthritis of various joints, such as the knees or elbows, and a few develop conjunctivitis, iritis, or dermatitis As has been previously stated, all cultures are negative including those for tubercle bacilli Sulfa drugs and penicillin are of no avail. However, arsenicals (e.g., neoarsphenamine 0 3 gm. intravenously every three to five days for a total of five doses) seem to be rather specific and bring about marked improvement and eventually cure. More recently streptomycin has been used with success. However, unless arsenicals or streptomycin are used the disease tends to run a protracted and incapacitating course of many months, and even after their administration cure is not always

dilatation of the upper urinary tract. In these cases, simultaneously with the disappearance or marked diminution in numbers of the L organisms in response to streptomycin therapy, there was subsidence of urinary symptoms, suggesting a causal relationship. In this series there were 9 cases of Reiter's triad syndrome, and an equal number with joint symptoms, but without conjunctivitis or ocular involvement. In 2 of the Reiter's cases a pure culture of L bacillus was obtained from knee joint fluid. All these cases showed a tendency to chronicity and to recurrence. One newly wedded couple developed acute arthritis a few weeks after marriage, and both had L bacillus infections of their genital tracts.

The evidence to date not only suggests that there are various strains of pleuropneumonia organisms, which vary in their pathogenicity to humans and also in their tendency to produce joint disease, but it also suggests that the condition may be contagious and transmitted venereally. However, some cases give no history of venereal exposure, and the gastro-intestinal tract is suggested as a portal of entry by the fact that a number of cases have had diarrhea just preceding the onset of the disease. These infections, including the ones showing Reiter's triad, are not susceptible to sulfa drugs or penicillin but are usually favorably affected by streptomycin, although evidence of joint inflammation may persist for some time. Occasional chronic cases are improved temporarily by streptomycin, but recur later.

The observed cases of pleuropneumonia infections have many similarities with cases of abacterial pyuria and Reiter's syndrome, which themselves are somewhat alike. Some of the points in common are: (1) Young males are predominantly affected. (2) Many but not all cases have a history of sexual exposure, whereas a few give a history of a preceding gastro-intestinal upset with diarrhea (3) There may be urethritis or cystitis, sometimes accompanied by polyarthritis or/and conjunctivitis—all of which tend to run a prolonged course unless given the proper treatment (4) There is pus but the usual cultures and smears are negative (5) Sulfa drugs and penicillin are not effective, whereas streptomycin is quite effective. (6) The complete cure may be slow, especially if the condition has been going on for a long time, in which case recurrences may take place after therapy. (7) The whole situation definitely suggests that pleuropneumonia organisms – possibly different strains, some of which have not yet been detected by present culture methods – may be the common cause of so-called abacterial pyuria and Reiter's syndrome However, the evidence as yet is not conclusive, and the situation needs further clarification.

NONSPECIFIC URETHRITIS (IN THE MALE)

The term "nonspecific" urethritis must have been coined in the days when just two kinds of urethral discharges were recognized—those that were gonorrheal in origin and those that were not—and this term is still used broadly to refer to all urethral inflammations of nongonorrheal origin However, among these urethral inflammations which are spoken of as nonspecific, there are some whose specific causes are known, such as those due to *Trichomonas vaginalis* infestation or to infection with pleuropneumonia ("L" bacillus) organisms Another type of irritative nonspecific urethritis follows the mechanical trauma of instrumen-

they are destroyed during the preparation of the slide. They can be recognized only by first growing them on rather special culture media, usually anaerobically, for two or three days, and then examining the tiny colonies microscopically *in situ* on the culture plate, using a special staining technic. In this way it can be seen that the cultures consist of tiny granules and fine filaments These swell to form soft spherical forms which again reproduce the granules and filaments. Though there is no doubt that this micro-organism differs in its properties considerably from most bacteria, it is felt that it is essentially a bacterium It is surmised that the culture method used is presumably not appropriate for all strains, and that as yet it is probably not successful in growing the organisms from all specimens in which they are present. There probably are many strains of pleuropneumonia organisms differing in pathogenicity, but the properties useful in differentiating strains of morphologically similar bacteria, such as growth requirements, serologic properties, etc, are as yet little understood

Clinically L organisms are found not uncommonly (6 to 26 per cent, according to various observers) in the cervical and vaginal secretions of apparently normal women without any history or evidence of genito-urinary disease. However their incidence is much higher (33 to 75 per cent) in women with inflammatory conditions of the genito-urinary tract, such as gonorrheal urethritis and endocervicitis (where they are found in association with gonococci, and often remain after the gonococci have disappeared), chronic endocervicitis, pelvic abscesses, etc Sometimes the organisms are found in pure culture, as in 2 Bartholin's abscesses reported, and sometimes in a mixed infection, but in far greater abundance than the other bacteria. In some cases the acute inflammatory condition developed a few days after sexual exposure, whereas in others there was no such history Acute arthritis in association with pleuropneumonial infection is much less common in women than in men, and the Reiter's triad syndrome has not been seen in women with such infection, so far as the author knows Thus it can be said that the fairly high incidence of L organisms in apparently normal female genital tracts would suggest that they are part of the common bacterial flora in this region Nevertheless, their much higher incidence in association with inflammatory conditions suggests that sometimes they may have a pathogenic action on the female genito-urinary tract.

When it comes to the consideration of males with pleuropneumonia infections, the picture is somewhat different Various observers have found pleuropneumonia organisms in as high as 20 per cent of men with so-called nonspecific urethritis, and the incidence of such organisms in apparently healthy males is quite low Furthermore in one series of 58 males in which the L organisms were found, every patient had evidence of prostatitis, urethritis, or other genito-urinary inflammation The cultures sometimes showed a pure growth of pleuropneumonia organisms, and sometimes a predominance of these but with also some other bacteria such as colon bacilli, staphylococci, streptococci, or diphtheroids Dienes and his co-workers described a number of cases of markedly acute cystitis with a stubborn, protracted course and tendency to recurrence, which closely resembled cases of so-called abacterial pyuria, and which gave a pure and abundant growth of pleuropneumonia organisms Sometimes there was

where it sometimes produces an irritating vaginal discharge. Every route by which males may acquire this infestation is not definitely known. There seems little doubt that it is frequently contracted through sexual intercourse with infested women. Nevertheless it is not always acquired through sexual contacts, and it is felt by some that infection may be transmitted from the anus or the mouth to the urethra. It has been seen in very young boys.

Many cases in which trichomonas is found have urethral strictures or abnormally small urinary meati. Commonly in addition to the trichomonas other bacteria are found in the urethral discharge, such as streptococci, staphylococci, and various bacilli. (Also in cases of gonorrheal infection, trichomonas is often found.) Frequently the prostate is also infested, which means that the urethral condition cannot be cleared up completely until the prostate has been rid of the trichomonas. As regards treatment, if any stricture exists it must be dilated to normal size, and if there is an abnormally small meatus it is enlarged by meatotomy, as it is felt that good urethral drainage is important in obtaining a cure. The author knows of no treatment as yet which is specific for trichomonas and decisively effective. Calcium mandelate, in the usual dosage to supply 3 gm. of mandelic acid four times per day, is said to be quite effective. Sulfonamide drugs and penicillin have been disappointing. Acetarsone vaginal suppositories have been successful in women, and the writer wonders if "mapharsen" in the usual doses might not be effective, but he has not tried it. Various urethral and bladder irrigations have been reported to be effective—potassium permanganate solution 1:4000, aqueous benzalkonium chloride ("zephiran") solution 1:10,000, 1 per cent gentian violet solution, 1:4000 solution of acriflavine in normal saline, "rivanol" dextrose, etc., but no one of them has apparently produced excellent results. Along with these irrigations, if the prostate is involved, it is massaged regularly. If bacteria such as various cocci and bacilli are also present, as they commonly are, it seems to make the condition more difficult to cure, and at best it tends to be chronic, with waxing and waning despite treatment, and with a tendency to relapse. For this reason patients with trichomonas infestation, even if doing well, should be kept under observation for many months.

Urethral discharges associated with pleuropneumonia ("L" bacillus) infections, with abacterial pyuria, and with Reiter's disease have already been considered.

Trauma, either mechanical or chemical, will produce a urethral discharge. Under the head of mechanical trauma come instrumentation and foreign bodies, such as a stone caught and impacted in the urethra or an inlying catheter. Chemical trauma is caused by the injection of strong solutions for prophylaxis against venereal infection or, to a lesser extent, by alcoholic excess. It is known that various bacteria, including staphylococci, streptococci, and *Micrococcus catarrhalis*, are frequently found in apparently normal urethras without causing detectable inflammation or disease. The mucous membrane of the anterior urethra is very sensitive and reacts to the slightest irritation with an outpouring of mucus, epithelial cells, and leukocytes. Thus the irritative type of urethritis following mechanical or chemical trauma is felt to result from the lowered resistance of the traumatized mucous membrane, permitting the bacteria present in the urethra to start an inflammation there. Nonspecific urethral discharge

tation or of an inlying catheter, or the chemical trauma produced when strong solutions are injected for venereal prophylaxis. In addition to urethral discharges of known infectious or traumatic origin, there are other urethral inflammations in the nonspecific category which truly deserve to be so classified because as yet no specific etiologic factor for them has been discovered. However, as the years go on undoubtedly more etiologic factors will come to light, so that the urethral discharges whose cause is unknown will constantly decrease.

In order to diagnose a urethral inflammation as truly nonspecific with no discoverable etiologic factor, those discharges whose cause is known will have to be considered in the differential diagnosis, and therefore they will be mentioned briefly

Diabetes mellitus will sometimes cause itching and slight inflammation about the urinary meatus with occasionally a little discharge Therefore, the urine should always be tested for sugar.

Gonorrheal urethritis can be diagnosed and differentiated by finding gonococci (gram-negative, intracellular, biscuit-shaped diplococci) in the smear of the discharge. In cases that are not fresh and acute, it is sometimes hard to find the gonococci, and several smears may have to be taken in order to find them Sometimes a special culture is necessary The discharge which has accumulated at the time of rising in the morning is most apt to be positive, and the patient can be given glass slides so that he can make these smears himself and bring them in for staining and examination.

The primary chancre of syphilis occasionally occurs intra-urethrally, and may give rise to a thin discharge Frequently these chancres produce no palpable induration, but if an indurated lesion is to be felt in the distal urethra, especially if it is ulcerated, syphilis should be suspected, and repeated darkfield examinations should be made Ulceration should be suspected in a patient showing any blood in his urethral discharge. The incubation period is from two to six weeks after exposure.

Occasionally a thin urethral discharge is encountered in association with and as a part of tuberculosis of the genito-urinary tract, and tuberculous strictures of the urethra may occur Since urethral manifestations are not seen until the disease is well established in other parts of the tract, e.g., the prostate, the diagnosis is not hard to make.

Infestation with the protozoon, *Trichomonas vaginalis,* frequently gives a milky urethral discharge In addition to the discharge, which is usually accompanied by itching and irritation, the patient may or may not have noticeable dysuria, frequency and urgency, and nocturia The diagnosis is established by finding the motile protozoon, which is nearer round than oval, of the same color as a leukocyte but definitely larger, and has several hair-like flagellae protruding from one end. A fresh preparation is made, either by a suspension of a drop of the discharge in a drop of saline on a glass microscopic slide or by taking a drop of the fresh warm urine, preferably the centrifuged sediment, and putting it on a slide. Under the microscope, the trichomonas can definitely be seen to move, in fact, their motility is what first calls attention to them The ordinary microscopic illumination is quite satisfactory, but the darkfield method is perhaps the best. This protozoon commonly infests the genital tract of women,

are found, they should be eradicated. As regards local treatments: Since stricture is found in more than 10 per cent of cases, the urethra is always calibrated, and if a stricture is found, it is dilated to normal size. Also if the meatus is tiny, it is enlarged by a generous meatotomy. It is important to do these things, as good urethral drainage is necessary for successful treatment. Whether the urethra needed dilatation or not, the weekly passage of a number 30 sound or dilatation with the Kollman dilator seems to help. This should be done after the instillation of 10 per cent argyrol solution or 1:5000 silver nitrate solution. The patient should report weekly, and is to instill 5 per cent argyrol into his urethra once daily. If a prostatitis is present, a weekly massage should be given, and the quantity of pus cells in the prostatic secretion checked microscopically. If urinalysis or culture indicates a possible focus higher in the urinary tract, further studies should be carried out, including intravenous or retrograde pyelography. If a focus is found, e.g., a pyonephrosis, it will probably have to be eliminated before cure of the prostatitis can be expected. Chronic nonspecific urethral discharges are almost always secondary to stricture or to pathology higher in the urinary tract, and in such cases no amount of treatment directed to the anterior urethra alone will cure them. Since their treatment is largely that of the factors causing them, and since nonspecific prostatitis is by far the commonest of these factors, that condition will now be considered.

NONSPECIFIC PROSTATITIS

There are various organs or regions of the body which seem to be "catch basins" for infections, exhibiting a tendency to acquire and harbor infections chronically. Examples of this are the tonsils, the apical region of the teeth, the sinuses, and the prostate. One supposes that the reason the prostate is prone to become infected and is often difficult to rid of infection is because it is composed of a complicated labyrinth of tubules and acini which by their very nature do not favor free drainage, and thus favor the occurrence and continuance of infection. Nonspecific prostatitis is fairly common, and is frequently secondary to some other focus of infection in the body from which the infecting bacteria are carried to the prostate by the blood stream. Such foci may be infected skin lesions as furuncles, infected tonsils, acute upper respiratory infections, and abscessed teeth, and especially the transitory bacteremia which often follows their extraction. The writer is reminded of an acute nonspecific prostatitis occurring in a friend following the extraction of an abscessed tooth A nonspecific prostatitis may also occur following the passage of instruments through the urethra Prolonged congestion due to excess of sexual activity, particularly when accompanied by alcoholic overindulgence, the presence of foreign bodies in the urethra or of stricture, and bodily chilling – all predispose to such an infection.

If the process is acute, there are fever and a throbbing pain in the region of the prostate, accompanied by frequency of, and rarely by difficulty in, urination, and usually cloudy infected urine. On the other hand, chronic nonspecific prostatitis often gives no obvious signs or symptoms, except some shreds in the urine or perhaps a slight urethral discharge, most noticeable on arising in the morning. The gland may be normal to palpation, but its secretion will show many leuko-

following excessive venery, which is often accompanied by alcoholic excess, is doubtless due to a similar cause. A similar type of nonspecific urethral inflammation appears within a day or two after intercourse but soon goes away. This may happen repeatedly with the same sexual partner, and the explanation given for this is that the vaginal secretions of certain women, especially immediately after menstruation, irritate the urethras of certain men.

Having mentioned the chief types of "nonspecific" urethritis, whose specific cause is known, truly nonspecific urethral inflammations will be considered, whose specific causes are unknown. For years these have been a minor bugbear of urologists, because they tend to be slow to heal, and, since nothing is known of their etiology, it is hard to put their treatment on a logical therapeutic basis and to do more than treat the signs and symptoms. Although many of these truly nonspecific urethral inflammations appear after sexual exposure, some appear without any such contact, in which case they are usually secondary to a nonspecific prostatitis which itself is secondary to some focus of infection in the body, frequently in the teeth or the tonsils. Cooper and MacLean cultured staphylococci from the discharge of 87 per cent of their series of 100 cases. It was the sole recoverable organism in 55 per cent, and was found associated with other bacteria, as streptococci, etc., in another 32 per cent. Since many cases of nonspecific urethritis appear after sexual intercourse, it is not surprising that the majority of cases occur between the ages of 20 and 40, which is the period of maximum sexual activity.

In the acute stage of nonspecific urethritis there is nothing that will produce *dramatically rapid cure Penicillin (aqueous suspension of crystalline penicillin* G with procain) 300,000 units intramuscularly twice a day for two days, and then once a day for five more days, sometimes helps, as at times does sulfadiazine The author has had no experience with streptomycin or aureomycin in such cases, but favorable results with aureomycin have been reported in a small series of cases In this acute stage gentle daily urethral irrigation with a tank and nozzle using warm normal saline or 1.8000 solution of potassium permanganate, and followed by the instillation of 5 per cent argyrol solution is beneficial. Sometimes the urethritis will subside rapidly and disappear, but it is apt to be quite persistent.

Pelouze found that two-thirds of several hundred cases of chronic nonspecific urethral discharge were due to the reaction of the mucous membrane of the anterior urethra to a focus of infection in the prostate or higher This finding is of interest in view of the fact that more frequently than not such a discharge is viewed as an indication of inflammation limited to the anterior urethra only, and treated as such without any consideration of the possible existence of an underlying focus of infection elsewhere, as in the prostate. This may account for the slow progress sometimes made in treating such cases Therefore in any case of nonspecific urethritis, even though it may be supposed to be limited to the anterior urethra, it is most important to search for any foci of infection and eliminate those found, in addition to giving treatment for the urethra. If the prostate is found to be the focus of infection, as occurs in about three-quarters of the cases, its infection in turn may very well have come from foci in the teeth or tonsils, and these also, therefore, should be investigated, and if foci

cystitis the symptoms are of longer duration and usually less acute. In these cases of bacterial infection, the mucosa of the bladder is injected and reddened, and in very acute cases the entire bladder mucosa is edematous and resembles red velvet, with shreds of fibrinous exudate. The urine contains plenty of pus cells and, according to the acuteness of the cystitis, from a few to many red blood cells. The colon bacillus is the most common causative organism.

Given a patient with the symptoms of bladder irritation, it is important to find out whether they are due to infection or to a bladder lesion, or possibly to both. The first diagnostic step, in both sexes, is to search for a urethral discharge and if such is found, smears of it are taken for Gram stain, and for culture for the gonococcus and the "L" bacillus. If there is no urethral discharge, or if the Gram-stained smear does not indicate gonococcal infection, the second part of a clean voided specimen in the male, or a sterile catheter specimen in the female, is taken for urinalysis—and especially for examination of the sediment—and also for culture. In the male, the first and second parts of the voided urine are collected in separate glasses or bottles for the two glass test as previously described (see p. 311). After this cystoscopy, including the estimation of any residual urine, is done. From the culture and the cystoscopy, the presence or absence of infection, or of a lesion, or of both can be determined. Since this article is concerned only with the treatment of infections, the treatment of any lesions found, e.g., carcinoma, will not be touched upon.

Suffice it to say that any stasis, such as that due to prostatic obstruction or to a large diverticulum of the bladder, and also any lesion, as a stone or a carcinoma, will prevent the eradication of any infection which might be present, and therefore must be eliminated before there is hope of curing that infection. Also if infection is present, the upper urinary tract must be investigated by means of intravenous urography and, if necessary, by cystoscopy with catheterization of the ureters and collection of urine from each kidney for analysis and culture, and retrograde pyelograms Obviously no amount of therapy will clear up the bladder urine of a patient who has a calculous pyonephrosis. If the upper urinary tract is normal, while the bladder is reddened and the urine contains pus but gives a negative culture, it is suggestive of an "L" bacillus infection, for which a special culture should be done. If the bladder contains small ulcers and is rather painful, and the urine contains both pus cells and red blood cells, yet the routine cultures are negative, tuberculosis must be thought of, and the upper urinary tract investigated, and urines taken for tuberculosis culture or for "guinea-pigging."

In cystitis due to nontuberculous bacterial infection, the infecting bacteria, having been identified, are combated with drugs and antibiotics according to the principles described earlier. As previously stated, the *colon bacillus* is the organism most commonly found. In acute cystitis in women hot saline vaginal douches often give considerable symptomatic relief, as do hot Sitz baths in the case of men. As an agent to make the bladder more comfortable, the author has a high regard for "Donnatal." This proprietary medicine contains hyoscyamine, atropine, and hyoscine as well as ¼ grain (15 mg.) of phenobarbital per tablet, and the author has found that one tablet four times per day is definitely soothing to irritated bladders. In acute cystitis, especially if there is fever, the

cytes when examined under the microscope Staphylococci, streptococci, or colon bacilli are the organisms commonly found on culture. Sometimes this prostatic infection gives rise to arthritis or to ocular lesions as iritis, which disappear after it has been eradicated. These may "flare up" and become temporarily worse after prostatic massages, especially following the first one or two

The present treatment of chronic nonspecific prostatitis seldom effects a cure rapidly and decisively, but instead usually moves rather slowly toward a cure which is not always absolutely complete, as evidenced by a common history of recurrences The main feature of this treatment is regular prostatic massage at intervals of from five to seven days, in order to promote drainage by expressing prostatic secretion. This can be frequently examined under the microscope for its pus content, and cultured as indicated A normal secretion should contain not over a dozen leukocytes per "high dry" field of the fresh wet secretion on a glass slide under a cover slip. Frequently the number of leukocytes cannot be reduced to an absolutely normal figure, but by treatment they can be greatly diminished to nearly normal The passage of sounds, instillations, and irrigations are frequently also used, especially if there is an associated chronic nonspecific urethritis The sulfonamide drugs have been disappointing in nonspecific prostatitis The disease is usually so mild that few patients have been hospitalized and given large doses of antibiotics regularly over the course of several days to a week However, large doses of penicillin thus administered should give improvement, if the infection is due to staphylococci or streptococci, and streptomycin should help if the infection is due to colon bacilli. The direct injection of 100,000 units of penicillin in 2 cc of saline into each of the two lateral lobes by a long needle directly through the perineum has produced encouraging results in a small series of cases with which the writer is acquainted. Sometimes the prostatitis cannot be eradicated until a primary focus in the teeth, tonsils, etc, has been removed, and a "focus hunt" should always be done in any case which is refractory to treatment or which recurs after it has been apparently cured

CYSTITIS

The symptoms of frequent, urgent, and uncomfortable urination indicate an abnormally irritated condition of the bladder The bladder irritation producing the symptoms may be due to a lesion such as carcinoma of the bladder, prostatic obstruction, the so-called Hunner ulcer in women, or to some other bladder pathology, and is frequently not associated with any infection of the bladder, in which case it may or may not be acute On the other hand, the irritation may be produced by bacterial infection of the bladder — a true inflammatory cystitis — and it also frequently is due to a combination of a bladder lesion with bacterial infection of the bladder This bacterial infection may have "descended" from one or both kidneys, it may have "ascended" from the urethra or prostate, or it may have been accidentally introduced by instrumentation, such as catheterization or cystoscopy In acute inflammatory cystitis the onset is rapid, and the symptoms acute and often accompanied by malaise and fever, whereas in chronic

measured by the excretion of phenolsulphonphthalein and of dye used for intravenous urography. By the time several months have elapsed after the conclusion of the pregnancy, the dilatation of the renal pelves and ureters has practically disappeared, unless some other pathologic condition interferes.

The etiology and routes of infection in pyelonephritis of pregnancy are the same as those already described for acute pyelonephritis in the nonpregnant. In addition there are other possible etiologic factors, such as constipation which is almost always present in pregnancy. There are those who believe that sometimes bacteria may by some mechanism get from the bowel into the urinary tract, and that this tendency is increased by constipation. The writer is inclined to doubt this, but it may be so. Another possible accessory etiologic factor is the severe anemia which sometimes occurs in pregnancy and which undoubtedly lowers resistance. Frequently the teeth are in poor condition in pregnancy, and dental sepsis is common and may act as a focus of infection.

The clinical incidence of pyelonephritis in pregnancy is 1 to 3 per cent according to various observers. The colon bacillus is the commonest invader found, with the staphylococcus the next most common. The maternal mortality rate is low. The few deaths that do occur from pyelonephritis in pregnancy are usually in women who have become depleted by a long illness, and who have had no relief from their kidney infection either by the proper treatment or through termination of their pregnancy. In such cases it is frequently found that the long illness has been due to some complicating factor in the urinary tract, such as an obstructing stone or an infected hydronephrosis, which was not diagnosed and therefore not treated. Children born at term are perfectly normal, even though their mothers have had acute pyelonephritis during the pregnancy

The effect of pregnancy on any pre-existing infection of the upper urinary tract is to increase it and cause a recurrence of the acute process, and those patients who have chronic pyelonephritis, possibly from a previous pyelonephritis of pregnancy, will probably have an acute exacerbation during pregnancy, unless effective countermeasures are taken. The kidneys of these people show the pathologic picture of a combination of the lesions of acute and chronic pyelonephritis with inflammatory scarring and diminution of the lumen of the arterioles. This process, if continued, eventually leads to renal insufficiency and sometimes to hypertension. Insufficiency and hypertension are especially apt to develop if, in addition to the chronic pyelonephritis, toxemia of pregnancy exists. In such cases the prognosis for a long life is not good.

Although in general the signs and symptoms of acute pyelonephritis in pregnancy are the same as in the nonpregnant state, nevertheless they have a tendency to be less definite and therefore less easily diagnosed. Furthermore the pregnant woman is frequently bothered by abdominal discomfort and complaints due to distention from the enlarging uterus, with the result that symptoms due to infection of the urinary tract are sometimes mistaken for these other complaints or for acute appendicitis, pneumonia, or pleurisy. However, the same methods and criteria described and used in establishing the diagnosis of acute pyelonephritis not associated with pregnancy — a careful history and

patient should be quiet and should take plenty of fluids. With the proper therapy, acute cystitis is usually much better in two days. However, the medicine should be continued longer, as already mentioned under the treatment of infections, in order that the bacterial eradication shall be complete and that, there will be no recurrences. In the case of a bladder lesion, e g, carcinoma, which cannot be eradicated, accompanied by an infection, it is reasonable to try to reduce this infection to a minimum with the proper drugs in order to decrease the irritation and make the patient more comfortable. However, under these circumstances, it will probably be impossible to eradicate the infection completely.

PYELONEPHRITIS OF PREGNANCY

The pyelonephritis occurring during pregnancy seems worthy of special discussion because its course is modified by the stasis engendered in the upper urinary tract by the pregnant state In pregnancy it is normal for the kidney pelves and the ureters to become dilated above the brim of the bony pelvis The dilatation is definitely more marked in primiparas than in multiparas, and makes its appearance between the fourth and sixth month in primiparas, but from the seventh month to the end of pregnancy in multiparas.

Formerly it was felt that the pressure from the enlarging uterus was the sole cause of this dilatation However, it is now considered that, while this plays a definite part, an equally important rôle in producing this dilatation is played by the hormones present in pregnancy, which act to diminish the tone of the smooth muscle and increase the capacity of the urinary tract

In this connection the experimental work of van Wagenen and Jenkins is of interest Working with a series of pregnant rhesus monkeys, whose period of gestation is six lunar months, they found that a few of their monkeys did not develop dilatation of the ureters and kidney pelves during pregnancy, as revealed by intravenous urography, but that the majority of them did In those showing dilatation, abdominal hysterotomy was performed, the fetus being removed, but the placenta not being removed or injured. This was done at times varying from the third to the fifth month, and the placenta was not expelled for a period of from 15 to 90 days thereafter The dilatation of the urinary tract was observed by means of repeated intravenous urography until some time after the placenta had been expelled It was found not only that the removal of the fetus and the consequent shrinkage in the size of the uterus had no effect on the dilatation of the ureters and kidney pelvis, but also that the dilatation persisted – and in some cases increased – until after the placenta had been expelled, when it soon returned to normal This is strong evidence that hormones present in pregnancy play just as important a role in producing dilatation of the upper urinary tract as does direct pressure from the enlarging uterus.

It has been observed in patients by Crabtree and Prather and others that when infection occurs the degree of dilatation of the ureters and kidney pelves is definitely increased over that normally found in association with pregnancy. The renal function of severely infected kidneys is definitely diminished as

measured by the excretion of phenolsulphonphthalein and of dye used for intravenous urography. By the time several months have elapsed after the conclusion of the pregnancy, the dilatation of the renal pelves and ureters has practically disappeared, unless some other pathologic condition interferes.

The etiology and routes of infection in pyelonephritis of pregnancy are the same as those already described for acute pyelonephritis in the nonpregnant. In addition there are other possible etiologic factors, such as constipation which is almost always present in pregnancy. There are those who believe that sometimes bacteria may by some mechanism get from the bowel into the urinary tract, and that this tendency is increased by constipation. The writer is inclined to doubt this, but it may be so. Another possible accessory etiologic factor is the severe anemia which sometimes occurs in pregnancy and which undoubtedly lowers resistance. Frequently the teeth are in poor condition in pregnancy, and dental sepsis is common and may act as a focus of infection.

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physical examination, urinalysis and urine smear, and urine culture and intravenous urography if available — will lead to the correct diagnosis of the same disease when associated with pregnancy.

"An ounce of prevention is worth a pound of cure," and the pregnant patient should be put on a regimen to reduce the liability to pyelonephritis The single most important prophylactic measure is to have her drink a dozen glasses of fluid every day to insure a good flow of urine and thus combat any tendency to urinary stasis In addition, great care should be taken to keep the bowels open and regular Regular dental care, a liberal diet with especial reference to blood-building factors, and plenty of rest are all important in maintaining a good general condition and resistance to infection At each visit to the obstetrician, a freshly voided specimen of urine should be examined, and if there is any doubt as to the presence of infection, a sterile catheter specimen should be obtained for sediment and culture. If an infection is discovered early in pregnancy before dilatation of the urinary tract has appeared, it is much more easily cured then than later. Also, if an infection is recognized early in any stage of pregnancy, even if it is not possible to eradicate it completely until after delivery, by proper therapy it can be prevented from ever becoming acute and giving clinical symptoms The exact medication to be given depends upon the bacteria present, and has been described earlier However, once the infection has been reduced to a minimum, it should be held there by a small but constant dose of a mild urinary antiseptic, such as one tablet of "mandelamine" four times per day, for the duration of the pregnancy

If acute pyelonephritis develops during pregnancy, the treatment indicated is the same as that for any acute pyelonephritis, with additional features on *account of the dilatation of the ureters and kidney pelves The patient is given* much fluid orally or intravenously, alkalies, and the drug appropriate to the infecting organism, exactly as described earlier under the treatment of acute pyelonephritis In addition, she is put to bed, lying prone with only one pillow and no headrest, and kept there until she has been free of fever and symptoms for several days The prone position is important because in the upright or sitting position the already impeded renal drainage is further embarrassed by the descent of the kidneys Also some believe that it is well to lie much of the time on the side opposite the infection, so that the uterus will tend to fall away and thus lessen any pressure on the ureter at the pelvic brim With the powerful urinary bactericidal agents available nowadays the above treatment usually suffices to bring about a cure or at least a marked improvement in a few days Formerly, however, the fever often did not come down even after several days, pain in the affected kidney continued unabated, and the patient was very sick Under these circumstances, she was cystoscoped and a good-sized ureteral catheter introduced into the pelvis of the involved kidney, which was then lavaged thoroughly with saline or 1 per cent silver nitrate solution or potassium permanganate solution As soon as the catheter "decompressed" the pelvis, the pain disappeared, and the temperature and the pulse fell toward normal. Sometimes the catheter was left in for constant drainage, but more often it was removed, to be reinserted again if pain in the kidney and fever returned Usually this was not necessary, but frequently it was done two or three times Occa-

sionally this procedure is still done, although such a necessity is rare nowadays. Although spontaneous abortion sometimes occurs at the height of an acute febrile attack due to urinary infection, cystoscopy and ureteral catheterization do not cause miscarriages.

The therapeutic interruption of pregnancy on account of pyelonephritis used to be limited to those few extremely acute and fulminating cases which resisted all usual forms of treatment, and where it appeared to be necessary in order to save the mother's life. However, since the serious end results of many cases of chronic pyelonephritis have been recognized, the indications for this procedure have been broadened to include cases in which there has been such severe renal damage from an uncured chronic pyelonephritis that it would be dangerous to the mother's life or longevity to allow the pregnancy to go to term. Other indications for this are pyelonephritis with acute exacerbations or becoming bilateral and severe, where toxemia appears in addition to acute pyelonephritis, or where, in the presence of acute pyelonephritis, there is evidence of renal failure or of rapid failure in general health.

If, after a few days of adequate therapy – forced fluids, alkalinization, the proper drug for the attacking bacteria, and rest prone in bed–the patient is not better, it is well to suspect that some factor, such as a calculus blocking the ureter, is preventing the treatment from being effective. If it has not already been done, a plain abdominal x-ray followed by intravenous urography is indicated. This will probably reveal the pathology, but if not further urologic investigation must be carried out. Rarely nephrectomy is necessary, as in the case of an acute pyonephrosis.

Since the dilated ureters may not recede to normal size for several months, it is even more important than in the pyelonephritis in the nonpregnant first to give the patient a thorough therapeutic attack with the proper drugs, followed by a milder urinary antiseptic for several months. The writer favors one tablet of "mandelamine" four times per day. When the urine has become clear, it is well to wait at least two weeks before giving any medicine, and then to have a urine culture If this is negative, it should be repeated again in a month to make certain that the infection has really gone. These precautions are taken because there is much to indicate that the pyelonephritis of pregnancy, if not cured, may become a serious, recurrent, progressive disease with dire consequences.

OTHER URINARY ANTISEPTICS

In addition to the agents already mentioned which act as potent antibacterial urinary antiseptics, there are a number of other excellent urinary antiseptics which will now be described:

Sulfonamide Drugs

Sulfanilamide and sulfapyridine are no longer used, and sulfathiazole is falling into disuse on account of its tendency to give sensitivity reactions such as skin rashes, coryza, "drug fever," etc.

Sulfadiazine The use of sulfadiazine, which is quite effective against colon

bacilli, and to some extent against aerobacter and the staphylococci, has already been described.

Sulfacetimide. Sulfacetimide, an acetylated sulfanilamide, which the writer likes less than sulfadiazine, is a popular urinary antiseptic. It is rapidly eliminated by the kidneys in good concentration in the urine in which it is readily soluble, whether the urine is acid or alkaline. It is quite effective against colon bacilli Although not usually toxic, occasionally it gives rise to malaise and cyanosis, but seldom to anemia, and it is for these reasons that the author does not like it as well as sulfadiazine to which toxic reactions are rare. The usual dose is 1 gm. four times a day

Sulfathaladine Sulfathaladine (phthalylsulfathiazole) when given orally almost sterilizes the bowel of colon bacilli and, therefore, is widely used in intestinal surgery as a prophylaxis against accidental infection Its toxicity is low. It is poorly absorbed from the intestinal tract regardless of dosage, and therefore does not attain more than a low concentration in the blood and the urine Nevertheless, it is effective against colon bacillus infections of the urinary tract, sometimes succeeding where other sulfa drugs such as sulfadiazine have failed The usual dose is 1 or 2 gm four times a day The acidity or alkalinity of the urine is not felt to be of importance. Sulfathaladine is not usually considered effective against other organisms in the urinary tract than colon bacilli.

Sulfasuxidine. Sulfasuxidine, like sulfathaladine, is a form of sulfathiazole (succinylsulfathiazole) and also resembles sulfathaladine in that it is poorly absorbed from the intestinal tract and attains only a low concentration in the urine Although it is chiefly employed to sterilize the intestinal tract at the time of bowel surgery, it has occasionally been used as a urinary antiseptic against infections with the colon bacillus Recently Crowley and O'Connor have reported success in eradicating stubborn colon bacillus infections of long standing by the simultaneous use of sulfasuxidine and streptomycin in a series of cases which had not yielded to treatment with streptomycin alone or with other drugs alone One gram of streptomycin a day was given for five days. Sulfasuxidine, 1 gm four times a day, was given some days before, during, and for several months following the administration of the antibiotic The urine culture usually became negative at the conclusion of the streptomycin administration, and never became positive again There were no important toxic reactions on taking 3 or 4 gm. of sulfasuxidine per day for a period of several months Crowley and O'Connor were certain that the simultaneous administration of the two agents was the reason for the success in these chronic stubborn cases, although they were unable to explain the mechanism They wondered if a transfer of colon bacilli from the bowel into the urinary tract might not somehow take place, and if so, whether the favorable effect might not be due to sulfasuxidine's greatly decreasing the number of colon bacilli in the bowel available for this transfer This might then permit the natural immunity of the individual to complete the eradication of the infection (The writer doubts this explanation for these successful results, but admits he has no better one)

Combined Sulfonamide Therapy (Sulfa-Combination) Before the prevention of massive crystalluria during the administration of sulfadiazine by forced fluids and alkalinization was generally adopted, serious complications were not

infrequently caused by extensive precipitation of crystals of the acetylated drug in the ureters, kidney pelves, or even the renal tubules, the last being usually fatal. Since these complications were obviously dependent on the solubility, or insolubility, of the sulfa drug in the urine, ways of increasing the solubility were studied. It was found that, if two or three different sulfonamides are present simultaneously in urine, each retains its own solubility uninfluenced by the presence of the other. Thus a saturated urinary solution of sulfathiazole can still be fully saturated with sulfadiazine and also with sulfamerazine, each compound behaving as though it were present alone and exerting no influence on the solubilities of the others. However, the situation is different as regards the antibacterial action of these mixtures, as they show a cumulative, additive highly antibacterial effect roughly equal to the total sum of all the sulfonamide drugs present Thus a mixture composed of half dosages of sulfadiazine and of sulfamerazine is more soluble and gives definitely less crystal formation than either drug administered alone in the same total dosage, but nevertheless gives an antibacterial effect roughly equal to the total dosage of all the sulfonamide drugs present.

As regards the development of sensitivity, if sensitization to one of the drugs in a mixture develops, it is almost always accompanied by sensitization to the other. From this point of view it would probably be preferable to use a mixture of sulfadiazine and sulfamerazine rather than one of sulfadiazine and sulfathiazole, owing to the greater tendency of sulfathiazole to evoke sensitivity. Since, with forced fluids and alkalinization, crystalluria is no longer a problem when administering sulfadiazine, the writer has never used these mixtures of sulfa drugs. However, he can imagine patients with cardiac insufficiency and edema in whom the forcing of fluids and the use of alkalies, particularly those containing sodium, such as sodium bicarbonate or sodium citrate, would be undesirable. Therefore, in administering sulfa therapy to such patients, a mixture such as equal parts of sulfadiazine and sulfamerazine might well be the treatment of choice.

"Mandelamine"

"Mandelamine," the brand name of the chemical compound methenamine mandelate, formed through the union of mandelic acid and methenamine, has been used with considerable success against a fairly wide variety of infections caused by colon bacilli, staphylococci, and streptococci. However, mixed infections, infections with *Aerobacter aerogenes* or the proteus bacillus and other urea-splitting infections are apt to be resistant, but occasionally are favorably affected Carrol and Allen have used it with success in cases of so-called abacterial pyuria. "Mandelamine" is not classified as a "strong" drug as each tablet contains only slightly more than 0 1 gm. each of mandelic acid and methenamine. It has no toxic effects, and therefore can be given for periods of weeks or even months without having the patient under supervision. For this reason, it is particularly adapted for use after a patient has gone home, as a urinary antiseptic to "follow-up" the stronger drugs given in the hospital in order to eradicate the last vestiges of postoperative kidney or bladder infection, postcatheterization cystitis, or following transurethral prostatic resection The usual schedule is three

tablets (which do not have to be dissolved) four times a day—after each meal and at bed time—for two weeks or a month If success has not then been achieved, it may be repeated for another month The intake of fluids should not go above 2500 cc. per 24 hours, which is no restriction in most cases, and the pH of the urine should be tested three times daily. Usually the action of the drug itself keeps the urine acid, but should the pH stay consistently above pH 5 5, a urinary acidifier, such as 1 gm four times a day of either ammonium chloride or acid sodium phosphate, is indicated The author has the highest regard for "mandelamine," and sometimes its administration for a month or more has proved efficacious where more powerful drugs have failed. However, in such circumstances, undoubtedly the elapse of time allowed for healing of the tissues has often played an important part in getting rid of the infection.

HEXAMETHYLENAMINE (METHENAMINE U S P —"UROTROPIN")

This is one of the oldest of the urinary antiseptics Its bactericidal action is due to the liberation of formaldehyde in acid urine. The urine must be definitely acid, with a pH not above 5 0, in order to liberate the formaldehyde Ammonium chloride is effective in producing this urinary acidity, unless a urea-splitting infection is present, while sodium acid phosphate is somewhat less effective Because it is a less potent urinary antiseptic than mandelic acid, the sulfonamide drugs, the antibiotics, etc, methenamine has fallen into disuse which is not entirely deserved It is most useful as a prophylaxis against infection, to prevent exacerbations of infections, or for use postoperatively where the tissues have not yet healed completely and infection is still present, and where a mild non-toxic drug is desired which the patient can take at home for weeks at a time without the need of medical supervision, as in the case of the sulfonamides To be effective in any given case, it must be possible for the urine to be made acid It is used against both bacilli and cocci, and occasionally succeeds in eventually eradicating the infection after more potent agents such as streptomycin have failed It is extremely irritating to gastric ulcers, and must not be given in such cases The usual dose is 7½ to 10 grains (0.5 to 0 6 gm) four times a day It comes in the form of tablets which should be dissolved in a glass of water. Ammonium chloride, 7½ grains (0 5 gm. [preferably enteric-coated]) is given four times a day with each dose of methenamine. The ammonium chloride does not have to be dissolved In place of ammonium chloride—although it is not as effective—acid sodium phosphate 10 grains (0 6 gm) four times a day is sometimes given.

Hexylresorcinol ("caprokol") is another mild urinary antiseptic which is also supposed to be calming to irritated mucous membranes To use it most effectively, it is necessary to reduce the fluid intake to 1000 cc or lower, which is undesirable in any acute infection of the urinary tract The dose is 0 3 to 0 6 gm , in capsules, three times a day.

"Pyridium" ("Serenium"—"Mallophene") is a pyridine compound which is stated to have a definite soothing effect on inflamed mucous membranes, although it is doubtful if it has any value as a urinary antiseptic The dose is two tablets which do not have to be dissolved, three times per day. It gives the urine an intense orange color.

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Modern Laboratory Technics in Urology

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WILLIAM WALLACE SCOTT, M.D., PH.D.

INTRODUCTION

IN THE LAST few years numerous laboratory technics have been incorporated into the urologic armamentarium. The material presented here is an attempt to record in brief fashion the use and evaluation of some of these modern laboratory technics in the diagnosis and treatment of certain urologic conditions. It is not intended to record in detail specific laboratory procedures but rather, whenever feasible, to make reference to standard laboratory texts and articles in the recent literature Arbitrarily these laboratory technics have been separated into two broad divisions, *chemical* and *physical*. With such broad division, omission is obvious and overlapping to be expected. In the handling of this material an effort has been made to present these newer views in proper proportion and to be neither offensively elementary nor bewilderingly advanced.

CHEMICAL LABORATORY TECHNICS

THE ENDOCRINES

Time and space do not permit an elaborate review of the chemical advances made in the isolation of gonadal, pituitary, and adrenal hormones. Primarily, this phase will be discussed only as it relates to urology.

Androgens Hormones which have the property of stimulating the development and maintenance of masculine sex characteristics, including deepening of the voice, enlargement of the external genitalia, as well as masculine distribution of hair, are known as androgens (from the Greek, meaning man-inducing) The most potent androgen so far discovered is testosterone, crystallized from testis by David and others in 1935. Evidence indicates that this compound is the major hormone of the testis, and that it is probably produced by the interstitial cells of Leydig.

In addition to its masculinizing action, testosterone, as well as certain other androgens, has certain general metabolic properties including the retention of many of the major components of the extracellular compartment such as nitrogen, potassium, phosphorus, sodium, and chloride.

Among many other androgens are androsterone and dehydroisoandrosterone, the former thought to be derived metabolically from the parent androgen, testosterone. Of the androgenic steroids, however, the esters of testosterone, e g, testosterone propionate, are the most powerful and clinically useful. This compound is marketed for parenteral administration in tablet and pellet form

and in sesame oil Methylation of testosterone results in a compound, methyl testosterone, which has masculinizing effects when given by mouth. Brief description of their use will be given below

Androgen Assay Methods. Unfortunately, there are no practical assay methods available for clinical estimation of blood androgens, although there is promise of several for the future (see below). Available methods afford determination of the amount of androgenic substance excreted and tell little of the amount of androgen manufactured and made available. There does appear, however, to be a fair correlation between urinary levels of androgen and observed masculinity, e g., urinary androgen levels of prepuberal boys are much lower than those of healthy adult men.

Bio-assay of urinary androgens may be carried out in several ways. At present, the most accurate is that described by Gallagher et al, in which the urine is subjected to acid hydrolysis, extraction with a lipid solvent, separation of androgens from estrogens, and determination of the amount of androgen by comparing with crystalline standards the amount of growth of the capon's comb resulting from application of the extract

Digression is necessary at this point to clarify thinking with regard to the so-called urinary 17-ketosteroids Certain steroids when allowed to react with meta-dinitrobenzene in an alkaline medium (Zimmerman reaction) give rise to a color which can be quantitatively measured in a colorimeter. Several of these steroids are active androgens, as determined by bio-assay, whereas others are not Hence, determination of urinary 17-ketosteroids is not synonymous with determination of urinary androgens, and is subject, therefore, to even greater drawbacks in the determination of male hormone deficiency However, colorimetric assay of urinary 17-ketosteroids has been of great value in endocrinologic research and in the detection of adrenal pathology (see below) With the aid of the compound digitonin, urinary 17-ketosteroids can be separated into alpha and beta fractions, the latter group being precipitated by digitonin Thus the alpha-ketosteroid, androsterone, can be separated from the beta-ketosteroid, dehydroisoandrosterone Until recently beta 17-ketosteroids were thought to arise solely from the adrenal This theory grew out of the finding of large amounts of this steroid in the urine of patients with adrenal cortical cancer That this is not strictly so is evidenced by the finding of lowered amounts of dehydroisoandrosterone after castration

Because of inadequate methods, most endocrinologists believe that the best criterion of male hormone activity is the observed state of development of the individuals' masculine secondary sex characteristics which are dependent for their initiation and maintenance on androgens

Pituitary Relationships There is clear-cut evidence for the dependence of the testes on pituitary secretions Hormones having action on the testes and ovaries are known as gonadotropins At present, it is believed that two pituitary gonadotropins exist in the male, one stimulating the production of androgen, the other stimulating the production of sperm, a situation somewhat analogous to that in the female where on gonadotropin, luteinizing hormone (LH), stimulates the development of the corpus luteum and another, follicle-stimulating hormone (FSH), stimulates the development of the ovarian follicle Presumably, in the

male, pituitary LH stimulates the production of androgen and FSH the production of sperm.

Removal of the pituitary leads to, among other results, atrophy of the testes with involution of the cells responsible for androgen and sperm production. Removal before puberty, like castration, thus results in a failure in development of secondary sex characteristics. Removal after puberty leads to less striking changes. In general, in the adult deprivation of androgen, whether by castration or hypophysectomy, rarely causes the voice to change back to its high prepuberal pitch or the phallus to atrophy, although body hair may lessen and the prostate shrink in size.

Removal of the testes in turn affects the pituitary. Briefly, anatomic changes occur and castration cells appear; functional changes occur, bio-assay of the gland revealing an increase in gonadotropin content of the pituitary itself which is reflected in a higher urinary gonadotropin level.

Gonadotropin Assay. As in the case of androgens, we are dependent upon bio-assay of urinary extracts to estimate gonadotropin production. These methods are relatively simple and, in general, consist of fractional precipitation of the gonadotropic material from the urine and measurement of the effect of this extract on the ovary and/or uterus of either the intact immature, or castrate adult, rat or mouse. Clinically, one such method (Klinefelter, et al.) has proved to be quite satisfactory in our hands. With this method, gonadotropic extracts of the urine of patients with pituitary insufficiency contain no gonadotropins, those of prepuberal boys contain only small amounts, less than 6 mouse units per 24 hours, those of healthy adult males from 6 to 52 mouse units, and those of castrates and patients with certain testicular tumors contain very large amounts, 52 to several hundred units per 24 hours.

It is necessary before concluding this phase of the discussion to call attention to the existence of another gonadotropin (variously known as prolan, A.P L. substance, or chorionic gonadotropin) obtained from the urine of pregnant women and in relatively large amounts from human placental tissue Unlike the gonadotropins present in the urine of castrate men and women and in the urine of women after the menopause – which appears to be identical, or nearly so, with FSH of the pituitary – chorionic gonadotropin is ineffective when tested upon normal monkeys or hypophysectomized female rats. Of importance to the urologist is the fact that chorionic gonadotropin appears in high concentration in the urine of men (and women) suffering from tumors containing chorionic tissue. This observation should be strongly considered in testing the urine of males with different types of testicular tumors

Estrogens. Hormones which have the property of stimulating the development and maintenance of female sex characteristics, including hypertrophy of the uterus and proliferation of its glands, vaginal changes, growth of the mammary glands, etc., are known as estrogens It is now generally believed that alpha-estradiol is the true estrogenic hormone Isolated by MacCorquodale et al from a sow's ovaries, and by Doisy and his associates from human pregnancy urine, this compound probably has its origin in the ovarian follicle. Unlike androgens, estrogens for the most part exert no appreciable effects on body growth.

Estrogenic substances have been obtained from a wide variety of sources including non-animal ones. Of great importance was the synthesis of diethylstilbestrol by Dodds et al in 1938 This synthetic compound exhibits an estrogenic potency several times that of estrone and is highly effective orally.

Estrogen Assay Methods As with androgens, no practical method is available for estrogens in blood and one must resort to the determination of estrogenic activity of urinary extracts for an estimate of estrogen production. Preliminary extraction of urine is similar to that for androgens except that more vigorous preliminary hydrolysis is necessary and that benzene extraction is more effective than extraction with certain other lipid solvents After separation into a phenolic fraction with alkali, bio-assay can be done in a number of ways. Some laboratories use the vaginal smear technic to determine estrus; others use the weight of the immature mouse uterus as an indicator of estrogenic activity In our laboratory the latter method has proved satisfactory. We use, without modification, the method of Evans, Varney, and Koch in which the increase in uterine weight of 21-day-old mice caused by dilutions of a urinary extract are compared with a standard uterine weight-dosage curve made simultaneously with crystalline estrone. Results are expressed in terms of units, a unit of estrogenic activity having been defined by the Commission on Biological Standardization of the League of Nations as the activity of 0.1 microgram of crystalline estrone Activity ratios for other estrogens have also been determined (Evans, Varney, and Koch)

Adrenal Hormones Review of the chemistry and physiology of the more than 20 crystalline steroids isolated from the adrenal cortex will not be attempted Numerous observations, however, point to a functional association between the adrenal cortex and the gonads In fact, many consider the adrenal cortex as the extragonadal source of androgens, particularly in the castrate. Both androgens and estrogens can be extracted from the adrenal cortex, and the urine of castrate males and females is found to contain both androgens and estrogens, though in reduced amounts. Of immediate clinical interest to the urologist is the excretion of certain steroids in high concentration in patients with adrenal hyperplasia or tumor This phase, as well as the laboratory *diagnosis of epinephrine-producing tumors of the adrenal medulla* (pheochromocytomas), is considered in the next section.

CLINICAL CONSIDERATION OF THE SEX ENDOCRINES

Hypogonadism

Clinically, recognition of hypogonadism (male hormone deficiency) is unmistakable under two circumstances (1) in the eunuch (castrate) where the testes are absent as the result of surgical removal, trauma, or congenital absence, (2) in males well beyond puberty who fail to develop masculine secondary sex characteristics in spite of the presence of testes in the scrotum. In this latter group, and in others where one may suspect androgen deficiency, laboratory determination of urinary androgens, *17-ketosteroids*, and *gonadotropins* may be of aid in establishing the diagnosis. By and large, one might expect to find considerable lowering of urinary androgens and 17-ketosteroids

with a high titer of urinary gonadotropins. Urinary gonadotropins might, however, be normal or low if androgen deficiency is secondary to pituitary failure.

It is in this group of patients, the true hypogonads, that androgens are properly used Gonadotropins, dependent on the capacity of the testes to secrete androgen, are useless in the case of the castrate or the severe eunuchoid whose testes are not responsive (Heckel). Androgens can be administered by the injection of an oil solution, by pellet implantation, and by mouth. The dosage required depends largely on the degree of androgen deficiency, the route of administration, and the androgen used. Twenty to 25 mg. of testosterone propionate in oil injected intramuscularly daily are adequate replacement for the most severe deficiency. Pellet implantation of this drug is more economical, requires replacement only at long intervals, and gives more even stimulation Testosterone propionate when given by mouth produces only slight clinical benefit. Methyl testosterone, when given in doses three to four times greater by weight than testosterone propionate given intramuscularly, induces somewhat comparable masculinizing effects (Hamilton).

The effects of androgen administration in the true hypogonad are both striking and gratifying. They consist primarily in development of masculine secondary sex characteristics. In the prepuberal castrate, administration of androgen leads to the development of a mature voice, the growth of hair with male distribution, growth of the genitalia with the exception of the testes, the ability to have an erection, and growth and secretion of the prostate and seminal vesicles Varying degrees of response are seen in the less severe hypogonad states whether prepuberal or postpuberal.

The Male Climacteric

Of recent years a great deal has been written about the decline of testicular function in the male past 50 years of age. It has been likened to the climacteric period of women (Werner). A multiplicity of symptoms has been assigned to this syndrome including *nervous symptoms* manifested by anxiety, depression, memory loss, headache, and lack of concentration; *circulatory symptoms* manifested by hot flushes, perspiration, palpitation, and vertigo; *general symptoms* of the nature of malaise with loss of drive and vitality. Such symptoms are said to be relieved by the administration of the male sex hormone.

Unfortunately, there are few objective tests which will indicate whether or not the above symptoms are due to testicular deficiency. In this connection. there are a few reports of an increased excretion of urinary gonadotropins in the aging male This is contrary to the experience of the writer, who has failed to find an increase in urinary gonadotropins in the aging male who has not been castrated surgically. Furthermore, I have never observed true hot flushes and profuse perspiration in the aging male who has not been castrated surgically.

Since the advent of surgical castration in the treatment of metastatic prostatic cancer, there has been ample opportunity to observe the effects of removal of the testes in the male past 50 years of age. In this group, true hot flushes occur and urinary gonadotropins increase, unassociated for the most part with anxiety, memory loss, lack of concentration, palpitation, vertigo, and loss of drive (Scott and Vermeulen).

By and large, the syndrome of the male climacteric has not be as a clinical entity, nor has the administration of male sex horme in a disappearance of the above symptoms (Vest and Barelare). Fir basis of available experimental evidence, estrogens will do a great than androgens in the relief of the hot flushes of the castrate and in t of urinary gonadotropins In this regard the observations of Hov interest. He observed that effective pituitary inhibition in the huma obtained with much smaller amounts of estrogen than of androgen. in a castrate male 1 mg of diethylstilbestrol every two days was the control of hot flushes and caused a drop in urinary gonadot above 96 to less than 6 mouse units per day; 50 mg. of testosterone every two days was not effective in reducing gonadotropins to 52 per day, the upper limit of the normal range.

Impotence

Impotence is a highly individual problem and often complex. Tl may affect erection, orgasm, or ejaculation, it may be purely symp may appear as a leading personality difficulty. It may be secondary urologic disease, male hormone deficiency, interference with nerv or it may be primarily the result of psychologic difficulties In dea gently with the problem, the status in all these fields must b accurately. By far the greatest number of patients seeking medical impotence is found to have no organic disease, but to have clear-cut problems. To such patients, administration of androgen is valueles its failure to improve the condition renders the patient refractory chiatrist's help It is the general impression among endocrinologists androgen deficiency exists, there is little chance that any sexual will result from androgen therapy, at least in doses which will produce such effects in patients with demonstrated male hormone Impotence of neurologic origin, as in tabes or after prostatic ope shown no improvement under androgenic therapy. Impotency may symptom in such conditions as myxedema and diabetes mellitus. I toration of libido and potentia follows shortly after correction of metabolic state

Cryptorchidism

Carl Moore first demonstrated that the scrotum functions as a "lo regulator" which effectively reduces the temperature of the testes a protects their spermatogenic function Testes which fail to des histologic evidence of degeneration of the seminiferous tubules aft For this reason efforts are made to bring the testes into the scro have consisted of medical and surgical procedures

After the classic demonstration by Earl Engle that gonadotro cause premature descent of the testes of young monkeys numero tions appeared indicating that they would also cause descent in hu

showing descent after treatment with gonadotropins varies from 16 to nearly 100 per cent. Thompson and Heckel, reporting descent in 20 per cent of their cases of cryptorchidism in all age groups, believe that higher values obtained by others result from the inclusion for treatment of cases of migratory and retracted types. They further point out that they were consistently unable to cause descent in most cases of true cryptorchidism. Pool, Cook, and Kepler were unable to induce descent with gonadotropins in any case in which the testis was retained within the abdomen or lay outside the normal pathway between the inguinal canal and scrotum.

The writer believes that the percentage of cases successfully treated with gonadotropins before puberty closely approximates the percentage of cases in which spontaneous descent occurs at puberty. For this reason, the recommendation is made that these children have an opportunity for spontaneous descent to occur, and if this fails, to cause descent by surgery. This view is further strengthened by reports of damage to the undescended testis following the administration of gonadotropins, this damage taking the form of extreme reduction in testicular weight as well as histologic changes in tubular structure.

Male Infertility

Of recent years more and more attention has been focused on the subject of male infertility. Any attempt at an understanding of the mechanisms involved must rest on a firm foundation of experimentation. The experimental literature is replete with evidence indicating that in all classes of vertebrates functional gonads are dependent upon pituitary secretion, and that gonadal defects secondary to hypophysectomy can be corrected by the administration of pituitary extracts There is evidence to indicate that gonadal defects resulting from vitamin B deficiency as well as inanition are secondary to alterations in pituitary activity (Mason and Wolf).

Largely as the result of the availability of crystalline androgens, attempts have been made to determine whether gonadal defects secondary to hypophysectomy could be corrected by administration of these testicular principles. Walsh, Cuyler, and McCullagh found that if androgen was given immediately after pituitary removal in the rat, testicular involution would not occur. Others (Nelson; Nelson and Gallagher) have confirmed this result and have extended their observations to show that the ability of a steroid to counteract the effects of hypophysectomy on germinal epithelium is not related to the androgenic strength of the substance. A weak androgen such as dehydroisoandrosterone was found to be more effective in this regard than testosterone (Papanicolaou and Marshall). Progesterone would also correct hypophysectomy changes (Selye and Friedman).

Perhaps because androgens can prevent the gonadal effects of hypophysectomy if given early, their effect on spermatic function in the intact animal was tested. In the rat, Moore and Morgan noted a curious inverse relationship between dosage and inhibitory effect. Under identical conditions, 0 05 mg of testosterone daily for 20 days caused a 60 per cent weight reduction in the testes, severe histologic damage, and complete cessation of spermatogenesis, whereas 1 0 mg. daily (20 times as much) was without appreciable effect The inhibitory effect of small dosages was reversible in that normal weights were established some

time after stopping the drug. They found the adult rat testis to be little affected by androgen

The effect of testosterone on the spermatogenic function of the normal adult human testis has not been sufficiently studied for comparison with experimental studies on the rat In general, it appears to be more readily depressed. For the most part, the effects of androgen on spermatic function in humans has been confined to patients suffering from a reduction in sperm count. Heckel found that the spermatogenic response to testosterone propionate of patients with oligospermia was irregular. Further reduction in sperms was usual although increases were noted When smaller doses of testosterone were given to patients with oligospermia, Rubinstein and Kurland noted increases in sperm counts. Much more information is necessary before we can assign to testosterone either an inhibitory or stimulating action of spermatic function Seemingly great importance rests on the age of the patient, the size of the dose of androgen, and the state of the pituitary. Unfortunately, few studies of the urinary gonadotropins have been made in the oligospermic patient. Such a study might lead to the finding of a depression of pituitary function in these cases.

Numerous eunuchoid males have received androgens in the treatment of their gonadal deficiency with little evidence of testicular growth and with no effect on the production of sperm The one exception in this latter regard is the report of Vest and Howard who noted the appearance of sperm in the ejaculate of a hypogonad male after the administration of testosterone. This is not a common finding

The results of gonadotropic administration in the oligospermic patient are equally equivocal Enthusiasm for this form of treatment has definitely waned Recently, a few reports have become available which indicate depression of spermatogenic function with estrogen administration McDonald, advocating estrogen in the treatment of hemospermia – a condition characterized by the presence of blood in the ejaculate – reported a reduction by two-thirds in the sperm count of hemospermic patients with normal pre-treatment values During treatment, the number of abnormal and nonmotile forms was increased fivefold. Following cessation of estrogen administration, there was a prompt increase to normal in number, form, and motility.

At best the treatment of the infertile male is difficult. Any evaluation in suspected cases of sterility should include complete study of both members of the sterile couple Evaluation of the male should include the taking of a careful history with emphasis on previous genital infections and injuries, any dietary deficiencies, exposure to irradiation, etc., a complete examination of the patient with special emphasis on the genital apparatus, a semen examination including determination of the enzyme, hyaluronidase, and often a testicular biopsy. For detailed accounts of the methods of semen analysis, interpretation of testicular biopsy, etc., the reader is referred to *Proceedings of the Conference on Diagnosis in Sterility*, edited by Engle, and to the writings of Hotchkiss.

At present, treatment should consist of correction of infections of the genital tract, dietary deficiencies, and, if possible, removal of obstructions to the passage of sperm The state of our knowledge of the role played by pituitary and gonadal hormones in spermatogenesis is not sufficiently adequate to permit recommenda-

tion of the use of these hormones in the treatment of the sterile male. This does not preclude the probability that endocrine substances will be useful in the future.

TESTICULAR TUMORS

Largely as the result of the excellent work of Friedman and Moore, the classification of testicular tumors has been greatly clarified. The reader is urged to consult their treatise on *Tumors of the Testis* which represents a detailed report of some 922 cases "collected at the Army Institute of Pathology between October 1940, when selective service began, and May 1946." It is unfortunate that in such a splendid series circumstances would not permit study of urinary hormones. Determination of urinary gonadal hormones would have done much to clarify this phase of laboratory diagnosis.

Much has been written concerning the amount of gonadotropic material excreted in the urine of patients with different types of testicular tumor but little regarding the distinct type of gonadotropin. It should be recalled that distinct types of gonadotropins exist. There is considerable agreement that chorionic gonadotropin, found in high titer in the urine of patients with chorionepitheliomas and in the urine of pregnant women, is entirely luteinizing and is ineffective on hypophysectomized female rats However, authors continue to speak of the extremely high titer of prolan A in the urine of patients with chorionepitheliomas, as it had always been used previously to refer to the follicle-stimulating hormone. For the sake of scientific advance, it is urged that attempts be made to determine the type of gonadotropic hormone excreted in the urine of patients with different types of testicular tumor as well as levels for urinary androgens, estrogens, and 17-ketosteroids. For methods of determining gonadotropins and gonadal hormones, the reader is referred to the article of Gustavson and D'Amour.

Generally speaking, studies of various investigators using the Aschheim-Zondek or Friedman tests for gonadotropins (which measure chorionic or luteinizing gonadotropin) indicate that gonadotropins increase in rough proportion to the embryonal character of the tumor. Chorionepitheliomas are associated with high titers, teratomas with adult features with moderate to low titers, and seminomas with low titers.

It is frequently stated that in addition to its diagnostic value, the Aschheim-Zondek test is of importance in judging the efficiency of treatment. Although this is often true, frequently false information is given. For example, if after removal of the primary tumor, roentgen therapy is given, the remaining testis may be damaged and result in a subsequent rise in urinary gonadotropin. This could be due to castration effect with rise in urinary follicle-stimulating hormone or to metastasis with production of chorionic or luteinizing hormone.

Approximately 1 per cent of the testicular tumors studied by Friedman and Moore were interstitial cell in type. Such tumors produce androgen, and it is important to study the urinary hormones of these patients, especially androgens and gonadotropins.

Finally, because of renewed interest in the site of estrogen production in the testis, it is advisable that all testicular tumors associated with feminizing changes be studied from the standpoints of their Sertoli cell content and their levels of urinary hormones (Berthrong et al.).

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Largely as the result of the excellent work of Friedman and Moore, the classification of testicular tumors has been greatly clarified. The reader is urged to consult their treatise on *Tumors of the Testis* which represents a detailed report of some 922 cases "collected at the Army Institute of Pathology between October 1940, when selective service began, and May 1946." It is unfortunate that in such a splendid series circumstances would not permit study of urinary hormones. Determination of urinary gonadal hormones would have done much to clarify this phase of laboratory diagnosis.

Much has been written concerning the amount of gonadotropic material excreted in the urine of patients with different types of testicular tumor but little regarding the distinct type of gonadotropin. It should be recalled that distinct types of gonadotropins exist. There is considerable agreement that chorionic gonadotropin, found in high titer in the urine of patients with chorionepitheliomas and in the urine of pregnant women, is entirely luteinizing and is ineffective on hypophysectomized female rats. However, authors continue to speak of the extremely high titer of prolan A in the urine of patients with chorionepitheliomas, as it had always been used previously to refer to the follicle-stimulating hormone. For the sake of scientific advance, it is urged that attempts be made to determine the type of gonadotropic hormone excreted in the urine of patients with different types of testicular tumor as well as levels for urinary androgens, estrogens, and 17-ketosteroids. For methods of determining gonadotropins and gonadal hormones, the reader is referred to the article of Gustavson and D'Amour.

Generally speaking, studies of various investigators using the Aschheim-Zondek or Friedman tests for gonadotropins (which measure chorionic or luteinizing gonadotropin) indicate that gonadotropins increase in rough proportion to the embryonal character of the tumor. Chorionepitheliomas are associated with high titers, teratomas with adult features with moderate to low titers, and seminomas with low titers.

It is frequently stated that in addition to its diagnostic value, the Aschheim-Zondek test is of importance in judging the efficiency of treatment. Although this is often true, frequently false information is given. For example, if after removal of the primary tumor, roentgen therapy is given, the remaining testis may be damaged and result in a subsequent rise in urinary gonadotropin. This could be due to castration effect with rise in urinary follicle-stimulating hormone or to metastasis with production of chorionic or luteinizing hormone.

Approximately 1 per cent of the testicular tumors studied by Friedman and Moore were interstitial cell in type. Such tumors produce androgen, and it is important to study the urinary hormones of these patients, especially androgens and gonadotropins.

Finally, because of renewed interest in the site of estrogen production in the testis, it is advisable that all testicular tumors associated with feminizing changes be studied from the standpoints of their Sertoli cell content and their levels of urinary hormones (Berthrong et al.).

time after stopping the drug. They found the adult rat testis to be little affected by androgen.

The effect of testosterone on the spermatogenic function of the normal adult human testis has not been sufficiently studied for comparison with experimental studies on the rat. In general, it appears to be more readily depressed For the most part, the effects of androgen on spermatic function in humans has been confined to patients suffering from a reduction in sperm count. Heckel found that the spermatogenic response to testosterone propionate of patients with oligospermia was irregular Further reduction in sperms was usual although increases were noted When smaller doses of testosterone were given to patients with oligospermia, Rubinstein and Kurland noted increases in sperm counts Much more information is necessary before we can assign to testosterone either an inhibitory or stimulating action of spermatic function. Seemingly great importance rests on the age of the patient, the size of the dose of androgen, and the state of the pituitary. Unfortunately, few studies of the urinary gonadotropins have been made in the oligospermic patient. Such a study might lead to the finding of a depression of pituitary function in these cases

Numerous eunuchoid males have received androgens in the treatment of their gonadal deficiency with little evidence of testicular growth and with no effect on the production of sperm. The one exception in this latter regard is the report of Vest and Howard who noted the appearance of sperm in the ejaculate of a hypogonad male after the administration of testosterone. This is not a common finding.

The results of gonadotropic administration in the oligospermic patient are equally equivocal. Enthusiasm for this form of treatment has definitely waned Recently, a few reports have become available which indicate depression of spermatogenic function with estrogen administration. McDonald, advocating estrogen in the treatment of hemospermia – a condition characterized by the presence of blood in the ejaculate – reported a reduction by two-thirds in the sperm count of hemospermic patients with normal pre-treatment values. During treatment, the number of abnormal and nonmotile forms was increased fivefold. Following cessation of estrogen administration, there was a prompt increase to normal in number, form, and motility.

At best the treatment of the infertile male is difficult. Any evaluation in suspected cases of sterility should include complete study of both members of the sterile couple. Evaluation of the male should include the taking of a careful history with emphasis on previous genital infections and injuries, any dietary deficiencies, exposure to irradiation, etc., a complete examination of the patient with special emphasis on the genital apparatus, a semen examination including determination of the enzyme, hyaluronidase, and often a testicular biopsy. For detailed accounts of the methods of semen analysis, interpretation of testicular biopsy, etc., the reader is referred to *Proceedings of the Conference on Diagnosis in Sterility*, edited by Engle, and to the writings of Hotchkiss.

At present, treatment should consist of correction of infections of the genital tract, dietary deficiencies, and, if possible, removal of obstructions to the passage of sperm The state of our knowledge of the role played by pituitary and gonadal hormones in spermatogenesis is not sufficiently adequate to permit recommenda-

accompanied by the characteristic symptoms of a typical spontaneous attack." In 1947, Calkins and Howard stated: "Our experiences with the use of the Roth-Kvale test coincides closely with theirs. In our patients the injection of histamine produced an abrupt rise in blood pressure which dwarfed that which accompanied the cold pressor test. The drug seemingly induced episodes which were in all respects identical with spontaneous attacks. The test appears to have a twofold value: first, as a method of producing attacks at will for study, and, second, as an indication of the presence of pheochromocytoma. Conversely, so far as known, no pheochromocytomata have been found in patients in whom the test was negative."

The introduction of a second test by Goldenberg, Snyder, and Aranow (1947) appears to be of equal, if not greater, significance than the histamine test in the diagnosis of pheochromocytomas. This test is based on the "adrenolytic" action (inhibition of response to epinephrine) of derivatives of benzodioxane. Specifically, such drugs as piperidylmethyl benzodioxane (933F), first investigated by Fourneau and Bovet, inhibit the blood pressure response of circulating epinephrine (injected or produced by pheochromocytoma); whereas in patients with essential hypertension, this drug has a predominantly pressor effect. Goldenberg and associates first established the value of this test in the diagnosis of 4 cases of pheochromocytoma. Their study included performance of the test on 28 patients with hypertensive disease, 14 normals, 14 normals with transient, epinephrine-induced hypertension, as well as the 4 patients with tumor. Recent unpublished data from the Medical and Urological Services of the Johns Hopkins Hospital confirm the importance of this test.

Hormonal Therapy of Prostatic Cancer

It is almost nine years since Huggins and his associates introduced the hormonal treatment of metastatic prostatic cancer. The rationale for treatment of this disease by castration or estrogen administration rests on basic prostatic physiology which indicates a dependence of the adult prostate gland on androgen production and the belief that prostatic cancer is an overgrowth of adult prostatic epithelium.

A wealth of evidence exists for the belief that prostatic growth is regulated by the hormone of the testis. Castration removes this hormone. Ample evidence is available for the belief that estrogen in proper doses will "neutralize" the effects of androgen. The belief that prostatic cancer is an overgrowth of adult prostatic epithelium is based on the fact that prostatic cancer epithelium retains the "adult character" of normal adult prostatic epithelium in producing the enzyme, acid phosphatase. Embryonal epithelium does not possess this characteristic.

Clinically, the effect of castration or estrogen administration is striking in the patient with metastatic prostatic cancer. Relief of pain, a decrease in the size and consistency of the local lesion, changes in osseous metastases even to their disappearance on the x-ray film, and gain in weight and strength have all been seen. The duration of these changes is varied. In his most recent communication, Huggins described the present condition of his original group of 21 patients castrated for metastatic prostatic cancer. Five were alive. Four showed no clinical or laboratory evidence of the disease. The period of survival was over five years.

Estimation of Urinary 17-ketosteroids in the Diagnosis of Adrenal Cortical Tumors

The physiologic significance of the urinary 17-ketosteroids is a problem which is still far from being solved It is the belief of certain investigators (including the writer) *that the greater portion of the 17-ketosteroids excreted in the urine* comes from the adrenal cortex, and that in the male the remaining, smaller portion is derived from the gonads. The evidence for these conclusions has been obtained from studies on castrate males and females, normal males and females, patients with Addison's disease, patients with adrenal cortical tumors or adrenal hyperplasia, males and females receiving hormone therapy, and patients with interstitial cell testicular tumors.

Generally speaking, the average value for adult men is 14 mg. 17-ketosteroid per 24 hours Adult females excrete 9 mg. per 24 hours Many workers feel that the difference of 5 mg in the two sexes represents the amount produced by the testes Further evidence in support of this concept is the markedly diminished excretion of urinary 17-ketosteroids in the female with Addison's disease. Often zero values are obtained. Males with Addison's disease excrete distinctly higher amounts indicating testicular contribution to the total level of urinary 17-ketosteroids.

Perhaps the greatest clinical significance attached to the determination of the urinary steroids is in the diagnosis of adrenal cortical cancer and adrenal hyperplasia In this connection the reader is referred to the works of Crooke and Callow, Warren, and Johnson In general, these authors have found increased excretion of urinary 17-ketosteroids in both adrenal cortical cancer and adrenal hyperplasia Values for adrenal cortical cancer were found frequently to be considerably higher than for adrenal hyperplasia. In the cancer group in the majority of cases, the predominant steroid was the beta-ketosteroid, dehydroisoandrosterone

In 1945 the writer studied the urinary steroids in a male, age 42 years, who had a proved adrenal cortical cancer associated with feminizing signs, including enlargement of the breasts and sudden loss of libido Prior to removal of the tumor, this man's urine contained upward of 200 mg total 17-ketosteroids per 24 hours, 95 per cent of which was the beta-ketosteroid, dehydroisoandrosterone Following operation the 17-ketosteroids fell precipitously to normal levels and there was restoration of the normal ratio of alpha and beta-ketosteroids

Tests for Tumors of the Adrenal Medulla (Pheochromocytomas)

In 1945 Roth and Kvale suggested the use of histamine as a tentative test in the diagnosis of pheochromocytomas (epinephrine-producing tumors arising from chromaffin tissue, frequently adrenal medulla) These investigators compared the blood pressure response and other clinical symptoms and signs following *intravenous injection of histamine* with *the effects produced by the cold pressor test in a* series of normal individuals, normal individuals who reacted hyperactively to the cold pressor test, established hypertensives, and patients with proved pheochromocytomas They found that "in the first three groups the blood pressure rose to a level somewhat less (with histamine) than the elevation obtained by the cold pressor test." In the 3 patients with tumor, the blood pressure "rose approximately 100 mm. more than the elevation obtained by the cold pressor test, and was

introduced as objective evidence of the course of prostatic cancer following treatment by castration or estrogen administration. Frequently, in metastatic prostatic cancer, serum alkaline phosphatase is elevated. Unfortunately, in occasional cases of metastatic prostatic cancer, serum acid phosphatase is normal and the test fails as a diagnostic guide. There are, however, no false positives, i.e., serum acid phosphatase is not elevated except in disseminated prostatic cancer.

Serum alkaline phosphatase, in addition to being elevated in prostatic cancer metastatic to bone, is frequently elevated in obstructive jaundice and diseases of bone associated with excessive osteoblastic activity, such as Paget's disease, rickets, osteoblastic sarcoma, and osteoblastic metastases to bone from carcinoma of the lung and breast.

TESTS OF RENAL FUNCTION

During the past two decades, renal physiologists have emphasized the importance of determining the individual functional capacity of the glomerular and tubular elements of the kidney. It is now possible to measure accurately glomerular filtration rates as well as rates of tubular excretion or reabsorption. These measurements have been made possible by the introduction of "clearance" tests, "clearance" having been defined as the quantity of blood cleared of a particular substance by the kidney per minute. The clearance method, introduced by Austin, Stillman, and Van Slyke, employing urea as the test substance, has been extended to include many other substances. Inulin clearance, introduced by Homer Smith, has largely superseded urea clearance as a means of measuring glomerular filtration rates. Inulin offers the advantage of being freely filtrable by the glomerular membrane, of not being metabolized, of forming no combination with the plasma proteins, and in being neither reabsorbed nor excreted by the renal tubules. Because of these properties it affords an excellent means of measuring glomerular filtrate rate. By comparison of inulin clearance with substances which have greater clearances than it has (creatinine, diodrast, phenolsulphonphthalein), tubular excretion can be measured, or if substances which have lesser clearances than inulin are used (glucose), tubular reabsorption can be measured. By means of clearance methods (usually diodrast) it is also possible to measure the rate of blood flow through active renal tissue.

For the most part these measurements have been developed and applied to the study of the mechanism of renal excretion and blood flow in the normal subject. Innumerable measurements have also been made in disease, however, in an effort to determine whether or not the process predominantly involves glomerular or tubular function, or whether the individual nephron (glomerulus and tubule) functions as a unit. In this regard Fishberg states: "In view of the diversity of pathological processes which implicate the kidney, one might anticipate conditions in which only *glomerular function* is impaired (glomerular insufficiency) and others in which tubular function is depressed (tubular insufficiency). Actually, however, uncomplicated glomerular or tubular insufficiency occurs only in exceptional circumstances."

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D AND ALKALINE PHOSPHATASES

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'hosphatases are enzymes capable of splitting the phosphate ion from organic ers of phosphoric acid. Inorganic phosphates are unaffected Although there numerous phosphatases present in body tissues, at present only two serum osphatases are of clinical interest. These separate enzymes are known as "acid" l "alkaline" phosphatases, because they have their optimum activity *in vitro* acid and alkaline pH (approximately 5 0 and 9 0, respectively).

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These phosphatases are readily determined quantitatively in serum and tissue chemical means and their location rendered visible by a histochemical method. reader is referred to the works of Bodansky, King and Armstrong, Gutman l Gutman, Huggins and Talalay, Bessey et al, and Hudson et al. for a detailed cription of serum phosphatase determinations, and to Gomori for phosphatase ning of tissues The King-Armstrong method, applied to both acid and alka- phosphatase determination, is probably the most dependable one in general today. It is a time-consuming technic, however, requiring multiple additions l transfers, precipitation and centrifugation of serum proteins, and two separate ed reactions. Later methods have increased the rapidity and ease of deter- iation, but difficulty has been encountered in maintaining the stability of the anic phosphate used as substrate.

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Acid and Alkaline Phosphatases

A description of the serum phosphatases is presented only as it relates to the differential diagnosis of urologic disease.

Phosphatases are enzymes capable of splitting the phosphate ion from organic esters of phosphoric acid Inorganic phosphates are unaffected Although there are numerous phosphatases present in body tissues, at present only two serum phosphatases are of clinical interest. These separate enzymes are known as "acid" and "alkaline" phosphatases, because they have their optimum activity *in vitro* at acid and alkaline pH (approximately 5 0 and 9 0, respectively).

Alkaline phosphatase was first discovered in intestinal mucosa and kidney and later in growing bone, cartilage, serum, and elsewhere. Acid phosphatase, discovered some 20 years later, was first found in the spleen and kidney and later in the prostate and serum.

These phosphatases are readily determined quantitatively in serum and tissue by chemical means and their location rendered visible by a histochemical method. The reader is referred to the works of Bodansky, King and Armstrong, Gutman and Gutman, Huggins and Talalay, Bessey et al., and Hudson et al. for a detailed description of serum phosphatase determinations, and to Gomori for phosphatase staining of tissues. The King-Armstrong method, applied to both acid and alkaline phosphatase determination, is probably the most dependable one in general use today It is a time-consuming technic, however, requiring multiple additions and transfers, precipitation and centrifugation of serum proteins, and two separate timed reactions. Later methods have increased the rapidity and ease of determination, but difficulty has been encountered in maintaining the stability of the organic phosphate used as substrate.

Phosphatase activity is expressed in units, the units varying with the particular method employed With the King-Armstrong method, considering the range of values reported by several laboratories, the normal range of serum acid phosphatase is from 3 0 to 10 0 units, with values above 10.0 considered abnormal and diagnostic. The range of serum alkaline phosphatase for the normal adult is from 5.0 to 10 0 (average 8 0) units, with values below 3 0 and above 13 0 considered abnormal

From a urologic standpoint, the observations of the Gutmans are exceedingly important These authors determined that in disseminated prostatic cancer, the serum acid phosphatase is elevated in the majority of patients, and that a marked rise indicates an unfavorable prognosis. These observations were confirmed and extended by Huggins and his associates, and serum acid phosphatase levels were

suspicious, and 3 clinically noncancerous; however, 2 of this latter group had benign papillomas of the bladder.

From these data it can be concluded that although a high percentage of correct diagnoses is made by smear, a negative laboratory report does not rule out cancer. A suspicious smear indicates clinical cancer in about half of the cases and is cause for extended clinical search for cancer, even if not immediately obvious clinically. False positive results occur but are reduced in number by repeated study of smears.

In summary, the authors caution against the clinical application of this method until a large series has been studied by a trained pathologist and until comparison is made with clinical data and biopsy material. Furthermore, they point out that the method is complementary, not supplementary. It appears that more data are necessary before this method can be applied as an accurate screening method for cancer of the urinary tract.

THE DETECTION OF CANCER CELLS IN THE PROSTATIC FLUID

Herbut and Lubin have applied the Papanicolaou technic to the detection of cancer cells in expressed prostatic secretion. In a series of 100 patients, cytologic diagnosis on smear was made 17 times. The diagnosis of cancer was confirmed by histologic examination of tissue in 10 of these 17, in seven it was not, although clinically suspected. In 2 cases of cancer of the prostate (one histologically evident, one clinically evident) smears were negative. In one case cancer was diagnosed on smear and not suspected clinically. All other positive laboratory diagnoses were made on smears from patients suspected clinically of having cancer. Work continues in their laboratory, as well as in others, and should in time provide sufficient data for accurate evaluation of this method.

UROLITHIASIS

In spite of a vast amount of clinical observation and research, the etiology of urinary lithiasis remains unknown This writer cannot attempt even a brief review of either the phase of clinical observation or experimental research but will call attention to papers which he considers fundamental in a study of the problem. First of these is the magnificent study of Prien and Frondel on the composition of urinary calculi. These authors point out that for many valid reasons, "the analysis of urinary calculi by chemical means is unsatisfactory," and proceed to analyze some 700 calculi by modern physical technics, including optical and x-ray crystallography. The results of their investigation showed that 67 1 per cent of the calculi were pure calcium oxalate (36.1 per cent) or mixed calcium oxalate-apatite (31 0 per cent), 19 5 per cent were pure magnesium ammonium phosphate hexahydrate, pure apatite and mixed magnesium ammonium phosphate hexahydrate; 6 1 per cent were uric acid (usually pure); 3.8 per cent were cystine (usually pure), 1.6 per cent were calcium hydrogen phosphate dihydrate. The oxalate stones were usually (but not always) found in sterile, acid urine, the phosphate stones were usually (but not always) found in infected, alkaline urine.

lar function) in 17 patients varying from "normals" with no urinary tract damage to those with severe renal dysfunction Comparable values of function were obtained in all patients but one. This author concluded that the thiosulfate test had no advantage over the phenolsulfonphthalein test, but that the latter possessed the great clinical advantage of simplicity. Recently, the accuracy of the 'phthalein test has been increased by insistence on proper hydration, complete urine collection, and photoelectric color measurement (Scardino and Scott).

Primarily because of urologic custom and relative ease of determination, blood nonprotein nitrogen levels are used as a measure of renal function It must be recalled, however, that the nonprotein nitrogen level of the blood begins to rise only after great reduction in renal function as evidenced by clearance methods When the blood nonprotein nitrogen is elevated, observation of its return to normal is of great clinical value, but when normal, finer tests of function should be made

By means of the intravenous pyelogram considerable evidence of renal function can be obtained at the same time one determines the existence of pyelographic evidence of disease processes of the urinary tract. By and large, good concentration of an organic iodide in five to 10 minutes after intravenous injection, as evidenced roentgenologically, means good kidney function. Furthermore, estimation by this means is applicable in cases where urine is difficult or impossible to collect — as after ureterosigmoidostomy

By omission of a discussion of dilution and concentration tests, as well as estimation of cellular elements, the writer does not mean to minimize their clinical importance. For a discussion of these methods the reader is referred to standard texts on laboratory methods

THE DETECTION OF CANCER CELLS IN THE URINE

In 1941 Papanicolaou and Traut demonstrated that uterine cancer cells could be recognized in vaginal and endometrial smears Subsequently, Papanicolaou and Marshall, Schmidlapp and Marshall, and Chute and Williams investigated the possibility of diagnosing cancer of the urinary tract by histologic examination of stained smears of urinary sediment. The study by Schmidlapp and Marshall of some 333 cases represents a continuation of the earlier study of Papanicolaou and Marshall, and in it all smears were read by Papanicolaou Because of Papanicolaou's great experience, this series probably represents the best results in the detection of cancer of the urinary tract obtained to date by this method. Comparison was made of Papanicolaou's reports of microscopic smears, classed as negative, suspicious, or positive, with the clinical evidence for cancer, classed as cancerous, suspicious, or noncancerous.

Of 198 patients showing no cancer cells in the urine, 176 (88.8 per cent) were clinically noncancerous, 8 (4 1 per cent) were suspected of having cancer clinically), and 14 (7.1 per cent) were found to have cancer clinically Of 53 patients showing suspicious smears, 24 (45.3 per cent) were clinically cancerous, 6 were clinically suspicious, and 23 clinically noncancerous. Of 82 patients showing positive smears, 71 (86.5 per cent) were clinically cancerous, 8 were clinically

tional 24 hours. If organisms continuing to grow in Brewer's cannot be isolated by aerobic subculture and anaerobes are suspected, anaerobic subcultures are made.

In the culture of the gonococcus and tubercle bacillus special media and methods are required. We use either Bacto-Proteose-Peptone #3 with supplements or Peyzer's media in culturing the gonococcus and Petragnini's, Dubos' and Corper's glycerol-egg media for the tubercle bacillus.

Following isolation of the specific organism, sensitivity of this organism to certain sulfonamides and antibiotics is tested. Dilutions of the drug in sterile trypticase soy broth are set up against the organism. If the organism is an anaerobe, Brewer's thioglycollate media are used in place of the soy broth. In reporting sensitivity, the tested organism is said to be sensitive to or resistant to a stated number of units of the drug.

The correlation between *in vitro* sensitivity and clinical action has not been adequately worked out, many factors such as individual antibody reaction, drug tissue level etc., complicating the picture. Varying opinion exists at present regarding the clinical value of sensitivity tests. Most bacteriologists, however, wish to see frequent testing done with the hope that the clinician will assist in correlating the *in vitro* and *in vivo* response

PHYSICAL LABORATORY TECHNICS

Photoelectric Colorimetry

Within the past 15 years a new physical laboratory tool, the photoelectric colorimeter, has been introduced into the field of analytic chemistry as the result of the development of the photocell or "electric eye." In the modern clinical laboratory the photoelectric instrument has replaced the visual instrument for multiple reasons, including (1) increase in accuracy of measurement by elimination of the subjective factor inherent in all visual comparative instruments; (2) increase in range of measurements, particularly accurate measurements of pale solutions upon which visual comparisons are impossible, (3) increase in the speed of measurement, (4) elimination of standard solutions necessary with the visual colorimeter Furthermore, in recent years almost all standard clinical laboratory determinations described employ the photoelectric instrument for color measurements. These methods include many of special interest to the urologists, such as the determinations of nonprotein nitrogen (Folin and Wu), phenolsulphonphthalein (Scardino and Scott), urinary 17-ketosteroids (Scott and *Vermeulen*), acid and alkaline phosphatase (King and Armstrong), hemoglobin (Malloy and Evelyn), and many others. There are several useful texts available at present on the subject of photoelectric colorimetry The writer has found Gebbs' work particularly good.

The Cystoscope

Largely unaltered in the last generation, the cystoscope has recently been improved by increasing the intensity of illumination with more efficient element material, and by increasing light transmission through the lens system by applying the principle of lens coating Furthermore, alterations in the angle of view

"Calcium carbonate, cholesterol, xanthine, and indigo were not found in a series of approximately 700 calculi."

Such accurate study throws great doubt on the reported composition of urinary stones determined by simple chemical means, and consequently the writer is hesitant to recommend any simple scheme of analysis. However, for several years we have used a combination of two tests (Seifter and Trattner; Simmons and Gentzkow)

Clinically, urinary stasis, infection, and gross nutritional deficiencies are recognized as playing some role in the causation of urolithiasis. According to Albright and Bloomberg, hyperparathyroid disease is a sufficiently frequent cause of renal lithiasis for its presence to be investigated Such study should consist of measurement of serum calcium and phosphorus, plasma protein estimation, and accurate determination of the calcium excreted. Although it is well known that urinary calculi are frequently found in association with hyperparathyroidism, as an etiologic factor, hyperparathyroidism is uncommon. Various estimates range from 0.2 to 0.8 per cent.

Since 1941 numerous articles have appeared implicating citric acid as a factor in the formation of urinary stones composed of calcium salts (Kissin and Locks, Scott, Huggins, and Sellman, Shorr et al.). It has been found that citrate binds calcium ions forming a soluble, weakly ionized complex. This enables salts of citric acid to dissolve stones and bone in the test tube Albright, Sulkowitch, and Chute have taken practical advantage of this effect in the solution of urinary calculi by lavage with buffered citrate solutions.

Little of significance can be added to the above. Intensive research, primarily from a physicochemical viewpoint, in the writer's opinion, is necessary if the etiology of urolithiasis is to be determined.

BACTERIOLOGY

Though not strictly under the heading of chemical laboratory technics, brief mention will be made of certain bacteriologic methods of relatively recent origin, designed to replace the trial and error method of application of urinary antiseptics to the treatment of bacterial infections of the kidney and urinary passages These remarks are particularly applicable to the diagnosis and treatment of urinary infections not associated with obstruction

Initial study should consist of determination of the causative organism by both aerobic and anaerobic culture and Gram's stain. The reader is referred to the text of Schaub and Foley for details. In general, the urine specimen, obtained by a sterile technic, is centrifuged, the sediment streaked on blood agar and desoxycholate plates, the remainder placed in a tube of Brewer's thioglycollate media, and all incubated overnight. If growth appears on the plates, cultural characteristics are noted and if the organisms are the same as in Brewer's medium, the culture may be reported If not, those organisms on Brewer's must be subcultured in order to isolate additional organisms. If the plates are negative and Brewer's media show growth, a smear and gram stain should be made to determine the type of organism and subcultured accordingly. If Brewer's media and plates show no growth, plates are discarded, and Brewer's are held for an addi-

urologic diagnosis the exact science that it is. Improvements in roentgenography continue to be made. In 1942, Morgan introduced his automatic x-ray timer based on the earlier development of a photocell sensitive to x-rays. This, coupled with the continuous moving grid, developed by P. C. Hodges and Morgan, has made possible consistently uniform exposures and has eliminated the necessity of depth measurement, both of which improvements simplify the technic. The development of faster and better film now permits shorter exposure with less radiation and greater detail. Of great interest in the future will be the progress made in rapid development of x-ray films (along the line introduced by Land for ordinary photographic film), the Schmidt camera, already applied by Morgan and his associates to the diagnosis of gastric lesions, and progress made in the intensification of the fluoroscopic screen. Space does not permit discussion of the use of various contrast media in combination with roentgenography in the diagnosis of urologic disease. Excellent treatment of the subjects of *intravenous* and *retrograde pyelography* may be found in the work of Wesson and Ruggles, of *cysto-urethrography* in the work of Kerr and Gillies, of *aortography* in the works of Dos Santos, Nelson, and Doss, of *perirenal air insufflation* in the works of Carelli and Sordelli, Quinby, Roome, and particularly Cahill, and of *angiography* (in animals) in the work of Trueta and his associates. It appears to the writer that the technics of aortography and perirenal insufflation of air furnish a great deal of information and involve little risk to the patient when conducted by one skilled in the procedure. Renal angiography in animals, if not in man, should continue to contribute greatly to our knowledge of renal physiology (Goodwin, Sloan, and Scott).

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through a telescopic lens have made possible the inspection of all aspects of the bladder and prostatic urethra. Among several alterations in this sense those of McCarthy and of Vest are noteworthy. By ingenious arrangement of a hinged-mirror, controlled remotely by a lever similar to that used for raising and lowering the lid of the catheterizing telescope, in combination with his foreoblique lens, McCarthy has succeeded in using one lens to sight forward, sideward, and backward. Vest's forward-looking telescope has greatly improved inspection of the prostatic urethra, particularly apical prostatic tissue.

The Resectoscope

In recent years a number of modifications of the Stern-McCarthy resectoscope have been developed, including those of Nesbit, Scott, and Baumrucker. Primarily, the instrument has been modified so that it can be operated with one hand, leaving the other hand free for rectal palpation. Quite recently the standard Stern-McCarthy resectoscope has been made available in size 16F to permit its use in the resection of valvular obstructions in the infant. The recent construction of the resectoscopic sheath out of lucite rather than bakelite should prove of considerable value.

The Cold-Knife Resectoscope. According to those familiar with its use, "the greatest single improvement in the Braasch-Bumpus resectoscope was the addition of the irrigating knife" (Massey). This is said to increase visibility and to permit more rapid removal of tissue.

The Cystometer

In 1939 Lewis introduced his recording aneroid cystometer. One year later Landes described a similar recording instrument of the aneroid type, differing essentially only in minor respects, the latter recording on a circular rather than linear graph. Both instruments have retained the sensitivity of the water manometer but have eliminated the kymograph and smoked drum Both are electrically driven and employ an ink-writer; ease of operation has been greatly increased.

Miscellaneous

Among many other advances in endoscopic equipment are a splendid modification of the Ravich lithotriptoscope, the Council stone extractor, and the Ellik bladder evacuator.

The Cautery

Until recently only minor changes have been made in the design of electrosurgical units. According to most urologists, the introduction of the tube-cutting current for electroresection is a distinct forward step. The current permits finer cuts to be made with the instrument, resulting in less sear or tissue destruction adjacent to the line of cut with less postresection slough. Good hemostasis is still provided by most machines since the tube-cutting current can be blended at will with spark-gap coagulating current.

The Roentgen Ray

Perhaps no field of medicine is more greatly indebted to roentgenography than is urology. Cystoscopy and roentgenography in combination have made

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The Bone Bank and the Use of Homogenous Bone

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HOMOGENOUS BONE

LITERATURE

The first recorded use of homogenous bone was that of Macewen in 1880. He had discovered its value some years previously. Since that time there have been several cycles of special interest directed to the use of homogenous bone. The voluminous early literature on the transplantation of bone has been reviewed by Marchand (1901), McWilliams (1916), Neuhof (1923), Lexer (1924), and Ghormley and Stuck (1934).

McWilliams, whose bibliography is most extensive, was able to find reports of 23 cases in which living homogenous bone had been transplanted, and of 15 cases in which dead homogenous bone treated by boiling or antiseptics had been used. Good results were claimed in 13 of the 23 cases receiving living bone and in 6 of the 15 cases receiving dead bone. Lexer after extensive clinical experience concluded in 1925 that homogenous bone, because of its inferior power of regeneration, is not suitable for transplantation into a bed of ordinary soft tissue, but in subperiosteal or intra-osseous beds it can stimulate greater new bone formation than autogenous bone, also that the homogenous transplant preserves itself in a periosteum-free tubular bone defect, though it may, owing to atrophy, be inferior to autogenous bone in the living and functional reconstruction and may fracture without subsequent healing. It has been generally believed for many years that the homogenous transplant is inferior as grafting material to the fresh autogenous transplant.

Serviceable massive transplants of homogenous bone replacing sarcomatous bones and the adjacent half joints have been reported by Lexer, Kuttner, Wade, Ellmer and Schmincke, and Meyer, and May Failures of such joint transplants have also been recorded (Kausch used dead bone), and the frequent local recurrence of malignant disease has been an additional factor tending to discourage use of this formidable procedure.

Experimental Literature Considering the amount of experimental work that has been expended on the role of the periosteum, direct animal studies of the comparative utility of homogenous and autogenous transplants of bone are few. Macewen's experiment with dogs demonstrated the potential value of the homogenous transplant Brooks and Hudson reported 76.8 per cent success with homogenous transplants in dogs as compared with 84 5 per cent success with autogenous transplants. When young dogs were used, autogenous transplants were 100 per cent successful, as compared with 66 per cent in old dogs.



A



B



C



D

FIG 1.—Homogenous transplants (A) Direct transplantation, extirpation after 43 days, necrosis, erosion, appositional immature bone. (B) Direct transplantation, extirpation after 100 days, abundant immature bone replacing necrotic bone by creeping [illegible] following storage of [illegible]

[illegible] fibrosis of marrow.

Frangenheim conducted long survival experiments on young rabbits, involving transplantation of autogenous and homogenous bone, with and without periosteum, into a resection defect of ulna, and found in each case almost complete substitution of transplanted bone and restitution to normal external form in one year.

Davis and Hunnicutt transplanted autogenous and homogenous bone into resection defects in dogs. They reported that the autogenous bone, both with and without periosteum, lived and successfully filled the defect. Homogenous bone in the defect acted as a scaffold for growth of new bone, and was ultimately absorbed. The autogenous transplant tended to assume the size of the bone into which it was transplanted. With homogenous bone there was believed to be shortening of bone in which the transplant was placed.

Renewed Interest. In more recent years there has been a revival of interest in the use of homogenous bone as shown by the papers of Smith, Ghormley, Orell Inclan, Bush, Henry, and others relating to "bone banks." These authors reported the use of homogenous bone for especially difficult cases where autogenous transplants were not available, in such conditions as large bone cysts in children, congenital pseudarthrosis, osteogenesis imperfecta, and others The reasons for the relatively infrequent use of homogenous transplants in the past were hesitancy in their use without special laboratory data, the uncertainty of the fate of the graft in the new host, and the lack of a method of preservation to avail the surgeon of quantities of bone as needed.

At the New York Orthopaedic Hospital the need for larger quantities of bone became so apparent, particularly in the surgical treatment of the scoliotic patient under the direction of A. D. Smith and W. H Von Lackum, that the writers began, in late 1945, to study this problem

Histologic Appearance

Biopsy specimens were obtained from 12 fusion areas in which homogenous bone had been employed in man Microscopic studies showed the bone spicules to be dead, but they were surrounded by connective tissue cells and osteogenesis occurred by metaplasia of these cells The homogenous bone apparently furnished the framework and possibly local calcium for the formation of the callus and the new bone. The dead bone fragments were gradually being replaced by living bone tissue (Fig. 1, A-D).

These findings, including those in control material of autogenous transplanted bone chips, supported the findings of other authors, particularly Baschkirzew and Petrow, Phemister, Gallie and Robertson, Leriche and Policard, Greig, Key, Gordon, and Abbott, whose studies of autogenous transplants were similar. In the control autogenous transplants a small number of the original osteocytes was often present and normal in appearance at three weeks, but none of the homogenous cells was found to have survived.

Blood Grouping Irrelevant

Further observations showed that blood groups had no bearing on the fate of the transplants. In the series of 67 operations in which homogenous bone was used, records were kept of the blood groups and the Rh factor of the

kept at 0° to 1°C. up to a maximum of over three weeks in concentrated sodium chloride solution, in physiologic sodium chloride with addition of the mild antiseptics, chloroform and toluol; and later, using aseptic technic, in sodium chloride solution, in serum, in Locke's solution, and in Ringer's solution. Healing of all transplants thus treated was good in contrast with that following the use of incinerated bone and ivory. They considered their best method of preservation to be immersion in Ringer's solution at low temperature under aseptic conditions and believed such preserved bone superior to previously used substitute materials and other dead bone.

Kuttner (1911) employed massive transplants of cadaver bone with clinical success in 3 cases of chondrosarcoma, using bone which had been preserved 24, two and one-half, and 24 hours, respectively at 1° to 2°C. in sterile Ringer's solution, chloroform being added in the first case. Sterility of material was controlled in 2 cases by culture.

In his first book, Albee (1915) mentioned immersion in normal saline as a method of preserving bone for a short period He stated that he had satisfactorily preserved living and cadaver bone for 48 hours in vaseline or wrapped in vaseline gauze at 4° to 5°C. He considered freezing to be theoretically undesirable. He laid emphasis on the importance of using autogenous bone grafts whenever possible, as they are most reliable. We believe the use of paraffin oil and vaseline should be avoided because of the foreign body reaction expected at the site of residually adherent material. In Albee's last book (1940) there was no mention of any method of storing bone.

Haas (1925), in experiments on survival of isolated bone, removed two metacarpal bones from a dog, fractured each, placed one bone in a bottle in the refrigerator at about freezing temperature and kept the other at room temperature for a given time, then bound the pieces of each fractured bone together and buried them in the back muscles of the same dog. Five weeks later there were definite signs of proliferation in fractured bones that had been kept at freezing temperature for as long as five days. There were no signs of proliferation in those kept at room temperature for two days or longer, or in those kept seven and ten days at freezing temperature. Haas considered this to be a test of the vitality of osteogenic cells, but other interpretations are possible.

Smith (1937) in 2 cases kept bone in a refrigerator at approximately 4°C and then autoclaved it just prior to use. In another case (1942) he employed bone refrigerated 18 days without any further treatment except washing in saline before using.

Inclan (1942) using bone preserved at 2° to 5°C. in saline, or saline and blood, or citrate and blood reported good results in 24 out of 34 cases of autogenous bone transplantation and in 6 out of 8 cases of homogenous bone transplantation. In a discussion of Henry's paper in 1948, he stated that the number of his cases had increased to about 100 and that he was satisfactorily preserving bone one to two weeks in an ordinary refrigerator at 2°C.

Effects of Low Temperature on Tissues

Because foods, serums, and other perishables have been preserved at subzero temperatures, the authors thought that perhaps this method could be used to

donors and of the recipients. The postoperative course was not influenced by the compatibility or noncompatibility of the blood groups. Identical operations, whether employing homogenous transplants from individuals with compatible or noncompatible blood manifested no difference in the morbidity. Of 73 bone donors, the blood was compatible with the recipients in 27, noncompatible in 28, and in 18 the blood type was undetermined. These statistics indicate that blood typing studies are unnecessary when homogenous bone is to be used Determination of the Rh factor, which is a property of red blood cells, is likewise unnecessary

PRINCIPLES OF TRANSPLANTATION

Our investigations like those of others showed that regeneration in bone transplantation takes place appreciably only when the transplants are in contact with living bone, occurring chiefly by metaplasia of adjacent connective tissue cells Baschkirzew and Petrow, Brooks and Hudson, and Keith proved that age is important, in that transplantation was more successful in the young than in the aged. Benesch, Chance, and Glynn concluded that sulfonamides inhibit bone calcification. Carrel, Bucciante, and Strumia showed that washing or storing tissues in saline or Ringer's solution interfered with successful transplantation According to Abbott et al, fat in excess retards bone formation All investigators agree that cancellous bone is best for osteogenesis while cortical bone is best for stability Massive transplants of cortical bone in man are revitalized slowly, the substitution of new bone often being little evident below the surface at the end of one year.

Loeb's extensive studies on individuality differentials and transplantation both guided and substantiated some of our work. Among other writings relevant to the transplantation of bone may be mentioned those of Barth, Axhausen, Gill, McGaw and Harbin, Key, Groves, Murray, Urist and Armstrong.

THE BONE BANK

LITERATURE

Storage of bone prior to transplantation is an old problem Ollier in 1861 seeking an innocuous and useful low temperature for preservation of transplants, reported obtaining more voluminous growth of bone from transplanted periosteum taken from bodies of dead rabbits preserved at 2° to 5°C. for 18 to 24 hours than from animals kept at 15° to 20° C. Grohé, similarly in 1899, using periosteum taken from dead rabbits preserved as long as 100 hours at 0° to 4°C., obtained growth of bone following implantation into young rabbits Morpurgo soon thereafter reported experiments in which periosteum of young chickens after varying periods of preservation at three different temperatures, was transplanted to vascular comb and wattles of the same and other chickens The limits of life of the cells in storage as judged by formation of bone or cartilage, were 192 hours at temperature of 3° to 6°C, 168 hours at 15°C., and 100 hours for approximately normal hen's temperature of 40° to 41°C.

Bauer and Weil (1910), students of Kuttner searching for methods of preserving bone, did 50 transplantations on 45 dogs, using bones which had been

moistened with normal salt solution to keep them from drying out, and storing in the icebox was sufficient. If longer periods were desired, the grafts were stored in jars of yellow vaseline or sterile albolene in the coil compartment of a refrigerator. Webster (1944) was successful with most autogenous skin transplants which had been wrapped in pliofilm, then covered by vaseline gauze to prevent drying, and kept in a refrigerator at 4°C. Transplants preserved more than three weeks did not take. Matthews (1945) reported the successful use of autogenous skin grafts which had been stored for 21 days in a refrigerator at from 3° to 6°C. wrapped in tullegras surrounded by moist saline gauze and placed in screw-capped bottles.

Gross, Bill, and Pierce (1949) preserved arterial segments of aortas at 1° to 4°C. immersed in a balanced buffered solution of salts containing 10 per cent homogenous serum, penicillin, and streptomycin. Vessels kept in this solution after removal from donor animals were successfully transplanted into other dogs after storage as long as 42 days, and human vessels thus preserved were used in children with congenital heart disease, with promising results. Tissue culture studies showed that viability of fibroblasts was maintained for 35 to 40 days in blood vessels stored in this way.

Grafting of corneal tissue to the eye puts extremely exacting requirements on a transplant. Corneal tissue of rabbits according to the experimental work of Thomas was satisfactorily preserved at 3°C. for as long as three days in physiologic saline or four days in Hartmann's solution; but after freezing in liquid nitrogen and then preservation at −40°C., there was loss of viability of the tissue, for the corneas invariably became opaque and were replaced by fibrous tissue. Eyes of salamanders preserved for as long as seven days refrigerated at 4° to 6°C. were successfully grafted by Stone to give a functioning organ. Transplants kept at 0°C. eventually degenerated, and the rapidity with which they succumbed depended partially on the time they had remained in the refrigerator.

The oxygen consumption of bovine corneas was measured by Duane in order to test storage methods at low temperatures. When stored in a moist chamber over Ringer's solution at 4°C. or in oil at 15°C. the QO_2 of the corneas remained normal for seven days and then fell to one-fifth normal in 10 to 12 days, respectively. The corneal QO_2 was reduced immediately to one-fifth of normal by quick freezing and dropped to this level within four days when kept at −40°C.; there was no further respiratory depression up to 60 days' storage. Katzin reported that human corneas for the Eye Bank were preserved most effectively at 3° to 5°C. for three days in a moist chamber in which the eye was suspended above physiologic saline without ever being immersed in it.

By analogy with the most applicable of the cited experiments we may infer that osteogenic cells, when cooled by ordinary slow methods, will be best preserved at 3° to 6°C., that cells will remain in excellent condition during the first week, and that survival may be expected for three weeks at this temperature. On the basis of this reasoning and, even more important, because of the danger of multiplication of a few contaminating fungi or bacteria at this temperature, we place a limit of three weeks on the preservation of bone in the ordinary refrigerator.

assure a constantly available supply of bone. Guidance in seeking optimum temperature for preservation of bone was sought in various fields of biology. The reviews of Heilbrunn, Bělehrádek, Luyet and Gehenio, Breedis, and Tressler and Evers contain much of this literature.

Tissues of most animals do not survive slow cooling to temperatures lower, or more than a few degrees lower than 0°C. for any prolonged time. It appears that they die at a temperature slightly below the freezing point of their protoplasm, if not before. A few easily desiccated forms of life, however, including some spores, cysts, seeds, and most bacteria can approach absolute zero without being killed. Solidification only does not necessarily kill cells. It is the freezing of water with crystal formation within the cells which may do irreparable damage to them.

What are some of the experiments related to the problem under consideration? Lambert preserved embryonic chick and rat tissues in culture media at temperatures varying from 7 to 20°C. and found the most favorable temperature for maximum duration of life (20 days) to be 6°C. Tissues survived 10 days at 0°C. and only a few hours below −7°C., the freezing point of some of the tissues. Lake demonstrated pulsation of embryo rabbit heart muscle in Ringer-plasma medium after exposure to −5°C. for 30 minutes, but not after exposure to −7°C, where plasma froze.

By tissue cultures Hetherington and Craig demonstrated that life was preserved in fragments of chick heart muscle at 0°C. in Ringer-Tyrode solution for as long as 15 days. Subzero temperatures killed the cells within a number of hours. This was in agreement with the quoted experiment of Buccianti who could demonstrate no survival of heart muscle at −25°C. and only short survival of epithelium and fibroblasts of skin, which were the most resistant of a number of tissues tested. Simonin exposed fragments of embyros of the mouse, rat, and ox to several temperatures and by cultures found the survival periods to be 20 days, five days, and a "short time" for respective temperatures of 0°C., −5°C., and −15°C. Some tissues were more sensitive than others. Waterman showed by chorio-allantoic transplantation that chick embryos were preserved best at 5°C. After refrigeration for 22 days, epidermis, cartilage, bone, and some skeletal muscle grew, while all other tissues were dead. Death occurred quickly during storage at 0°C. In an earlier work with rabbit embryos, Waterman showed that bone and cartilage ranked with epidermis in surviving storage relatively longer than other tissues.

Carrel in 1912 reported transplantation of a newborn infant's skin which he had preserved some weeks in petrolatum at 3°C. He quoted Tuffier as having in 1910 and 1911 serviceably used fat, cartilage, and peritoneum which had been kept for periods of a few hours to two months in petrolatum in a refrigerator. Magitot at this time had with brilliant success transplanted a cornea which had been preserved in human plasma for eight days in a refrigerator at 4°C. In a discussion of Carrel's paper, Davis stated that he had successfully transplanted skin, fascia, tendon, bone and cartilage after preservation in an ordinary refrigerator or in cold storage. In 1940 Davis again stated that for the preservation of skin for grafting, he had experimented with refrigeration of various types. If the grafts were to be used within 24 hours, wrapping them in sterile dressings

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able to observe a characteristic living picture by vital staining. As a test for viability this may be open to some question. After short freezing the most malignant of the tumors could be grown in tissue cultures. Klinke stated that his findings were not characteristic of malignant cells, for similar growth was demonstrated with several normal embryonic tissues of chick. He mentioned successfully culturing kidney tissue of a six weeks old rabbit following freezing in liquid nitrogen Mider and Morton reported that squamous epithelium and connective tissue cells of a normal adult rat's skin sometimes remained viable on subcutaneous implantation following rapid freezing and storage for 24 hours at −74°C. Briggs and Jund obtained in young mice about 52 per cent takes of skin grafts which had been frozen one to 24 hours at −78.5°C. About two minutes were taken for cooling from 0° to −15°C. Similar grafts stored five and 10 days at 0°C. were grafted with only slightly less success, while grafts stored for 15 and 20 days failed.

Webster reported an interesting grafting experiment with frozen skin in a man. A control graft of freshly taken skin was 98 per cent successful at 21 days after implantation. A graft kept 17 days in Ringer's solution at 4°C. was partly lost at 21 days. A graft similarly treated but also lyophilized at −72°C. gave the appearance of an 80 per cent take at the 21 day period. Strumia and Hodge preserved human skin in plasma at −20° to −25°C. for periods of one to 61 days. Using this method for autogenous transplantation, they obtained 80.5 per cent takes as compared with 86.4 per cent in controls.

In contrast with the success obtained in grafting aortic segments which had been preserved at 1° to 4°C. in a special solution, Gross, Bill, and Pierce reported highly unsatisfactory results with tissue which had been kept frozen for two to 36 days at −72°C. Two dogs survived for at least six months, but 9 died following breakdown of anastomosis. Tissue cultures of dogs' aortas which had been stored at −70°C. led to growth in only 2 of 34 instances.

Keith froze bone chips of a dog in liquid air for 10 minutes. Roentgenograms taken subsequently to reimplantation showed only fair growth of bone, and the microscopic examination revealed only a small amount of newly formed bone. Keith stated that this finding was a surprise.

From the above literature pertaining to the preservation of various tissues at subzero temperatures one can make several observations in relation to bone. The ideal extremely rapid freezing and thawing, through the assumed critical temperature range of 0°C. to −40°C. is not possible because of the large size of the pieces of bone desired for use. Slower freezing and thawing, however, have been surprisingly successful with some tissues and have challenged instantaneous cooling and thawing as the only method for limiting formation of relatively large ice crystals. Although existence of latent life in mammalian cells has been demonstrated at very low temperatures by various investigators, only a small proportion of the total number of cells involved has survived some of the experimental conditions (Breedis) and then usually not for many days or even, as far as reported in some instances, for many hours. Survivals at extremely low temperatures have been less than those in the vicinity of −75°C. Mere survival does not indicate retention of power to function. The largest number of experiments with vertebrate life have been performed with neoplastic cells

ARGUMENTS FOR SUBZERO PRESERVATION

In keeping tissue for prolonged periods near 0°C. the hazard of multiplication of a few contaminating fungi and bacteria is very real. Mycelial forms of some fungi are killed in 24 hours at a temperature of −15°C At −18°C (0°F.) most of the fluid in the tissues is frozen solid, the danger of multiplication of ordinary contaminating bacteria, even on the surface, is negligible; diffusion of fluids is minimal, and chemical reactions, including the enzymatic and autolytic reactions, practically cease.

There is evidence that some animal cells do survive very low temperatures Mider and Morton, after rapid en masse freezing of several experimental rat and mouse neoplasms at −74°C for 24 hours, inoculated the thawed tissue into animals and obtained growth in a high percentage of cases. With saline cell suspensions rapid freezing was lethal and slow freezing gave relatively few takes Tumors arising from frozen material exhibited a lengthened latent period Breedis and Furth reported successful preservation of suspensions of various neoplastic cells in Tyrode's solution following slow freezing and storage for many days at −70°C. Rapid freezing was more injurious to the cells. Thawing prior to inoculation was rapidly carried out by shaking the tube container in water at 37°C Snell and Cloudman froze pieces of various neoplasms of mouse and rat to −75°C. and found, in agreement with the previous work, that most of the neoplastic cells were injured less by slow freezing than by rapid freezing. Breedis and Furth noted that many cilia of the epithelium of chicken trachea were actively motile at two, 16 and 327 days after preservation at −70°C.

For leukemic cells of mice, Breedis described a critical temperature range between 0° and −15°. If the fall in temperature through this range occurred in 12 seconds or less, the leukemic cell suspensions were completely inactivated. If it occurred in one minute or more the suspensions remained infectious. Below this range, the rate of cooling down to −196°C was immaterial.

For the vinegar eel, a nematode about 2 mm. long, Luyet and Hartung found the dangerous zone to lie between 0° and −40°C This is probably the maximum range of the dangerous zone for protoplasmic systems In their experiment, in order to avoid the deleterious effect of crystallization, this zone was traversed with great rapidity (at the rate of 1000°C. per second) from fluid state to solid amorphous "vitreous" state, and then with equal rapidity in the opposite direction during thawing. Motility could thereby be demonstrated following short immersion in liquid air Organisms more than several millimeters in diameter could not be expected to survive such treatment, as heat could not with sufficient rapidity be conducted from or to the interior This method was used by Hoagland and Pincus in an attempt to preserve human spermatozoa at −196°C. The number of motile organisms surviving more than two hours was small and not favorably comparable with the good survival rate over a period of days reported by Parkes for only a moderately rapid freezing and preservation at −79° and −196°C. Even after freezing at −20°C Parkes found some survival for a short period.

Klinke, by rapidly freezing pieces of tissue by direct immersion into liquid nitrogen and liquid hydrogen, kept cells of a number of neoplasms of mouse and rat deeply frozen at −196° and −253°C. for days and weeks, and was then

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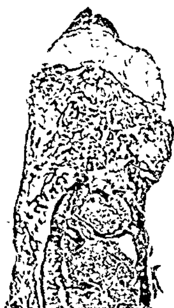


Fig 2.—Autogenous transplant, fresh, 28 days in animal 107. Result was graded as "excellent."



Fig. 3.—Autogenous transplant, frozen at −25° C for seven days prior to implantation, 21 days in animal 107. Result was graded as "excellent."



Fig 4.—Autogenous transplant, frozen at −25° C. for 14 days prior to implantation, 42 days in animal 108 Result was graded as "excellent."



Fig. 5.—[illegible]

larization of marrow in the transplant.

(J.A.M.A., 137:588, 1948)

and embryonic cells. These cells are particularly rapidly growing and so probably more tenuous of life than normal cells which we wish to preserve.

Human skin has been shown to be comparatively resistant to cold, and experiments with skin probably come closest to those reported in indicating what may be expected of bone. The experiments of Strumia and Hodge are most suggestive



FIG 6—Homogenous transplant, frozen at −25° C. for 84 days prior to implantation, 21 days in animal 103. Result graded as "fair to good" at low power. However, this high power view shows formation of abundant cartilage callus and metaplastic osteoid tissue adjacent to the necrotic eroded bone of the transplant.
(*J.A.M.A.*, *137*:588, 1948)

here, and if we try to preserve bone in its naturally moist condition in an air-tight container at −20° to −25°C., we may, perhaps, sufficiently approach their conditions and avoid inconvenient addition of plasma.

In the argument for subzero storage of bone in the frozen state we must admit that for practical purposes of grafting it may not be necessary to preserve the osteogenic cells in vigorous or even viable condition. This will be especially true if we are willing to accept something less than an ideally rapid take of the graft. The low temperature probably has its merit simply in stopping autolysis and bacterial growth and preserving most of the physical and chemical properties of the bone and its attached tissues in a little altered state. Subsequent findings lead us to believe, at least as far as homogenous transplantation is con-

cerned, that this is so, for no homogenous osteogenic donor cells, whether fresh or preserved by low temperature freezing, have been found to survive in the host.

Experiments. Putting the method of subzero preservation to test, experiments were undertaken to see what the tissue reactions would be to bone which had been preserved by freezing, whether autogenous or homogenous Young, nearly fully grown, rabbits were used. The ilium, being cancellous bone and readily accessible, was considered suitable for studying osteogenesis and tissue reactions. Bone of hemi-disk shape was removed from the margin of the ilium with a

TABLE I

ORDER OF HEALING OF TRANSPLANTS

	Healing	Index*
(1) Autogenous fresh	13/5	2 6
Autogenous frozen seven days	8/3	26 6
(2) Autogenous frozen 14 days	5/3	1.66
Homogenous fresh	6/4	1 5
[illegible]	4/3	1 33
(3) [illegible]	7½/7	1 07
[illegible]	2/2	1.0
(4) Homogenous frozen boiled	1/2	0 5

* T[illegible] denor[illegible] equal[illegible] good,[illegible] at least one side of the cortex and also extending up into the medulla for a short distance), 1 equals fair (transplant only fused to bed of host, with or without callus on one side of cortex) and 0 equals nonunion (or excessive peripheral resorption of bone and little formation of new bone)

circular saw, so that the bed and the transplant were always the same shape and size. Control studies were made with fresh autogenous and homogenous bone and with boiled bone. Both iliac bones were used so that one type of bone could be transplanted to one ilium and another or control type to the other ilium of the same animal, thus allowing comparative analysis of results The transplants were held in place by tantalum wire.

For the experiment proper, freshly removed bone was placed in storage bottles, preserved in a freezing cabinet at approximately −24°C. for periods of one, two, four, eight, and 12 weeks, and then transplanted The animals were killed at three and six week intervals, and the transplantation areas were studied grossly, roentgenologically, and microscopically. In this series 32 transplantations were made by 28 operations on 19 animals Results of the 29 transplants suitable for analysis are given in Table I where they are expressed in terms of a "healing index" (Figs 2-6)

Frozen bone transplants regularly became attached to suitably prepared beds of host bone and were slowly and at least partially replaced by new bone formed by the host through metaplasia and creeping substitution Fresh autogenous bone and autogenous bone preserved in a frozen condition for one week and even for two weeks were more quickly and completely reconstituted into bone approaching normal architecture than frozen homogenous bone, but there was little difference in favor of autogenous bone when preservation in the frozen

state was prolonged beyond 28 days. This suggests that possibly autogenous bone cells usefully survived freezing at −24°C. for one week and that some cells survived for two weeks. The possible effect of slow denaturization of autogenous protein is also to be considered. The homogenous bone cells, whether fresh or frozen, never grew in transplants; this bone served as a trellis and stimulus for growth of cells from the host.

In an additional longer term experiment, homogenous bone frozen 14 days was examined 84 days after transplantation to several animals. Bony union was



Fig 7.—Homogenous transplant, frozen at −25° C. for 14 days prior to implantation, 84 days in animal [illegible] and beginning creep[illegible] "excellent"

(*J A M A*, *137* 588, 1948.)

excellent The greater part of the original transplant still remained in a necrotic and somewhat eroded condition. About one-third of the margin was bordered by newly formed bone (Fig 7), and there was some creeping substitution.

Epiphyseal cartilage attached to bone which had been frozen for two weeks was necrotic when examined three or more weeks after implantation, and was noted to interfere locally with the formation of new bone Boiled autogenous bone transplants were inferior to frozen transplants, the medulla being poorly revascularized and devoid of new bone. The importance of re-establishing circulation in bone transplants is indicated by the inferior formation of new bone in several animals in which transplants had become angulated, thereby preventing revascularization directly from the medulla of the host.

The inclusion of boiled autogenous bone as a part of this experiment is not without merit in the establishment of a base line. Accidents in operating rooms have occasionally resulted in enforced use of such material, and with clinical

success. Numerous experiments with animals recorded in the literature have shown that boiled transplants can be made to succeed though they do so slowly as compared with fresh autogenous transplants (Marchand; Phemister; Gallie and Robertson; Key; Orell). The healing index of our homogenous frozen bone was in the same range as that of autogenous boiled bone, though slightly higher.

Sources of Bone

Large quantities of bone may be obtained from operations where bone is sacrificed, as in hip surgery, traumatic amputations, thoracic surgery, and many others. Cadaver bone may be used if procured in the safe period under sterile conditions. Suitable methods are needed for the sterilization of homogenous bone. According to the bacteriologic cultures of Bergmann, bone of cadavers (lower femur) remained sterile on the average for 12 hours following death *not due to generalized infection.* Lexer using this criterion subsequently encountered a streptococcus in a transplant removed 10 hours after death. Bacteriologic studies by Hunt and others indicate that in nonbacterial diseases postmortem invasion of blood does not ordinarily occur within the first 12 hours. In choosing a donor one had best be quite conservative here. Suitable cases of sudden traumatic death are potentially rich sources of sterile bone and should be satisfactory if removal can be performed in a surgical operating room within several hours after death. Sterility of such bone should be tested by cultures.

Zimbron at the meeting of the American Academy of Orthopaedic Surgeons in Chicago, in January 1949, showed his method of collecting cadaver bone. He had previously published a preliminary report of results in 25 operations on 23 patients who had received transplants of bank bone. In 14 patients the bone used was taken within the first eight hours from tibias of healthy individuals who had died in traumatic accidents. His bank bone was used within three weeks following preservation at −10°C. Two cases became infected by processes not attributable to the transplants No difference was noted between the behavior of transplants taken from live individuals and those which came from cadavers.

Bones from stillborn infants and infants of short survival have been used From a theoretical standpoint, the great potential for cellular growth characteristic of such cells has no value, for these cells of homogenous bone die in the host. On an equal weight basis, bone of the newborn contains only about half as much calcium as adult bone (Shohl). The proportion is still lower in fetal bone.

Precautions in Collecting Bone

The bone must be collected and stored under strictly aseptic conditions. There should be no history of recent infections, malaria, or jaundice. A negative serologic test for syphilis is required. Turner and Fleming showed that treponemata of yaws and syphilis retained their motility and virulence in rabbits after exposure to a temperature of −78°C. for at least three years. At −20°C. survival of treponemata of syphilis did not exceed two months. Olitsky et al demonstrated prolonged survival of a number of viruses in serum at −20 to −30°C.

Records are kept in a card index file such as shown:

BONE BANK

DONOR'S NAME:	HOSPITAL NO.:
SOURCE OF BONE:	WEIGHT OF BONE:* :
RECENT INFECTIONS:	HISTORY OF JAUNDICE:
SEROLOGY:	HISTORY OF MALARIA:
DATE STORED:	

RECIPIENT

NAME.	HOSPITAL NO.:
OPERATION	
DATE USED:	

* The weight of the bone is recorded chiefly to give an index as to the amount of bone present in the bottles.

At the New York Orthopaedic Hospital it has been the policy not to use bone until it has been stored for two weeks, during which time the donor has been assessed as free of infection Cultures are not made routinely, but as indicated.

PREPARATION OF BONE FOR STORAGE

All soft tissue and cartilage are removed from the bone prior to storage. The size of the transplant to be used is determined at the time of operation, therefore large pieces are stored. The bone is placed in sterile sets of dual bottles which are properly labeled (Fig 8) Such containers prevent contamination in the handling of the bone, evaporation, and sudden changes of temperature.

METHODS OF STORAGE OF BONE

Direct or Immediate Grafting. Bone may be obtained from other patients simultaneously treated by operation, or from relatives who are admitted to the hospital for this purpose, it may be transferred directly from the donor to the recipient. Our records indicate that this method of transfer has been used in 15 instances for homogenous transplants and in 9 instances for syngenesious transplants.

Delayed Grafting. Delayed grafting, whether autogenous or homogenous, involves the storing of bone in the tissues of a patient for use in secondary operations. This method has been used successfully in our institution on several occasions, but will rarely be necessary in hospitals which have instituted a method of preserving bone in a bank. Key (1928) and Moore (1949) noted successful results in the use of delayed grafts.

Refrigeration. This is a convenient method of preservation. For tissue which is to be used in man, the temperature and duration of storage are important.

(a) Ordinary Refrigeration (2° to 5°C.): Bone may be stored at this temperature for periods up to three weeks.

(b) Deep Freezing (−25°C. approximately): After this method was well tested through experimentation by the authors, it was instituted as the method of choice and has been in constant use since early 1946. Bone may be stored for an indefinite period by this method. One of the writers successfully used bone which had been stored for over one year.

success Numerous experiments with animals recorded in the literature have shown that boiled transplants can be made to succeed though they do so slowly as compared with fresh autogenous transplants (Marchand, Phemister; Gallie and Robertson; Key, Orell). The healing index of our homogenous frozen bone was in the same range as that of autogenous boiled bone, though slightly higher.

SOURCES OF BONE

Large quantities of bone may be obtained from operations where bone is sacrificed, as in hip surgery, traumatic amputations, thoracic surgery, and many others Cadaver bone may be used if procured in the safe period under sterile conditions Suitable methods are needed for the sterilization of homogenous bone. According to the bacteriologic cultures of Bergmann, bone of cadavers (lower femur) remained sterile on the average for 12 hours following death not due to generalized infection. Lexer using this criterion subsequently encountered a streptococcus in a transplant removed 10 hours after death. Bacteriologic studies by Hunt and others indicate that in nonbacterial diseases postmortem invasion of blood does not ordinarily occur within the first 12 hours. In choosing a donor one had best be quite conservative here Suitable cases of sudden traumatic death are potentially rich sources of sterile bone and should be satisfactory if removal can be performed in a surgical operating room within several hours after death. Sterility of such bone should be tested by cultures.

Zimbron at the meeting of the American Academy of Orthopaedic Surgeons in Chicago, in January 1949, showed his method of collecting cadaver bone. He had previously published a preliminary report of results in 25 operations on 23 patients who had received transplants of bank bone. In 14 patients the bone used was taken within the first eight hours from tibias of healthy individuals who had died in traumatic accidents. His bank bone was used within three weeks following preservation at −10°C Two cases became infected by processes not attributable to the transplants. No difference was noted between the behavior of transplants taken from live individuals and those which came from cadavers.

Bones from stillborn infants and infants of short survival have been used From a theoretical standpoint, the great potential for cellular growth characteristic of such cells has no value, for these cells of homogenous bone die in the host. On an equal weight basis, bone of the newborn contains only about half as much calcium as adult bone (Shohl). The proportion is still lower in fetal bone.

PRECAUTIONS IN COLLECTING BONE

The bone must be collected and stored under strictly aseptic conditions There should be no history of recent infections, malaria, or jaundice. A negative serologic test for syphilis is required Turner and Fleming showed that treponemata of yaws and syphilis retained their motility and virulence in rabbits after exposure to a temperature of −78°C. for at least three years. At −20°C. survival of treponemata of syphilis did not exceed two months. Olitsky et al demonstrated prolonged survival of a number of viruses in serum at −20 to −30°C

Records are kept in a card index file such as shown:

BONE BANK

DONOR'S NAME:	HOSPITAL NO.:
SOURCE OF BONE:	WEIGHT OF BONE*:
RECENT INFECTIONS.	HISTORY OF JAUNDICE:
SEROLOGY:	HISTORY OF MALARIA:
DATE STORED:	

RECIPIENT

NAME:	HOSPITAL NO.:
OPERATION:	
DATE USED	

* The weight of the bone is recorded chiefly to give an index as to the amount of bone present in the bottles.

At the New York Orthopaedic Hospital it has been the policy not to use bone until it has been stored for two weeks, during which time the donor has been assessed as free of infection. Cultures are not made routinely, but as indicated.

PREPARATION OF BONE FOR STORAGE

All soft tissue and cartilage are removed from the bone prior to storage. The size of the transplant to be used is determined at the time of operation, therefore large pieces are stored. The bone is placed in sterile sets of dual bottles which are properly labeled (Fig 8) Such containers prevent contamination in the handling of the bone, evaporation, and sudden changes of temperature.

METHODS OF STORAGE OF BONE

Direct or Immediate Grafting. Bone may be obtained from other patients simultaneously treated by operation, or from relatives who are admitted to the hospital for this purpose; it may be transferred directly from the donor to the recipient. Our records indicate that this method of transfer has been used in 15 instances for homogenous transplants and in 9 instances for syngenesious transplants.

Delayed Grafting Delayed grafting, whether autogenous or homogenous, involves the storing of bone in the tissues of a patient for use in secondary operations. This method has been used successfully in our institution on several occasions, but will rarely be necessary in hospitals which have instituted a method of preserving bone in a bank. Key (1928) and Moore (1949) noted successful results in the use of delayed grafts.

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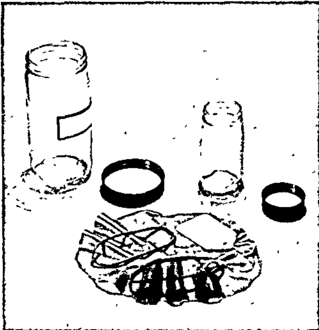


Fig 8A—A set of storage bottles with plastic screw caps, labels, rubber sheeting, and two rubber bands, assembled prior to wrapping and autoclaving

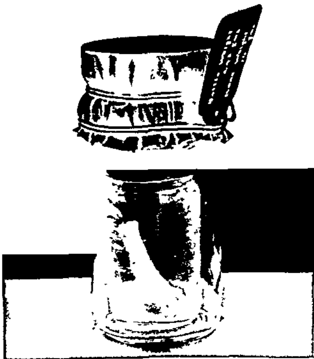


Fig 8B.—Sterile storage bottles containing bor

Merthiolate Bone Bank. Reynolds and Oliver have recently reported the preservation of bone in aqueous merthiolate. The bone is collected aseptically and placed in a solution of 1:1000 merthiolate for two weeks. The bone is then stored indefinitely in a 1:5000 solution which is changed every two weeks. Their experimental studies performed on long bones of dogs were convincing as to the success of this method. The method had previously been used with satisfaction by O'Connor and Pierce, and by Brown and McCarthy for the storage of cartilage. (Peer has reported on the preservation of cartilage in 50 per cent alcohol.)

Recent Clinical Results with Homogenous Bone

Wilson in 1947 reported the use, since early in 1946, of preserved frozen bone from 40 donors in 30 operations upon 25 patients. The bone, after preservation in a deep freeze unit maintained between −10° and −20°F. (−23° to −29°C.), was used as small chips to pack bone cavities or to reinforce various types of fusion operations, especially of the spine. No infections or foreign body reactions occurred. From a clinical standpoint he considered the results to be entirely satisfactory, and as near as could be determined by clinical and histologic study the behavior of such bone after transplantation was similar to that of fresh autogenous bone. In both cases the bone was resorbed and transformed into living bone entirely as the result of action of the host tissues. Wilson noted in 1948 that this method had been used in more than 50 cases. At the meeting of the American Orthopedic Association on May 19, 1949 he reported experience in over 200 cases with results which were highly satisfactory and compared favorably with those attained by the use of autogenous bone.

Alldredge, while in an Army General Hospital, collected bone from clean amputations and stored it in an ordinary refrigerator. The bone was placed in glass jars containing saline and sulfanilamide. The use of this bone was not great enough to warrant conclusions, but was sufficient to suggest further experimentation with the method. His series of cases proved that transplanted homogenous bone gave good results in a high percentage of cases. Fifteen cases were discussed more fully following Henry's paper.

Henry reported the use of homografts in children, particularly the use of dual grafts in tibial defects, and the discussion which followed indicated increasing use of homogenous bone, including bank bone.

Reynolds and Oliver reported 36 cases in which bone transplants preserved in merthiolate had been used. These included spinal fusions, arthrodeses, and repair of bone defects. These authors believed that the results were comparable in every way to those obtainable with fresh autogenous grafts. Drainage persisted in one case of active osteomyelitis and the grafts were removed in another case of osteomyelitis.

Weaver preserved homogenous bone in the frozen state from 49 operations on 46 patients. He noted shipping frozen bone packed in dry ice in two instances. The operations were varied in type. There was 100 per cent success in joint fusions and 72.5 per cent success in nonunions, while the entire group showed 82.6 per cent success. There was an infection rate of 8.1 per cent. The authors found very satisfactory results where chip grafts were used, but massive cortical grafts

were less successful. Weaver's conclusions, in an honest evaluation of his results, coincides with the writers', in that frozen homogenous bone has a definite place in orthopedic surgery but it also has its limitations.

Speed and Smith, in their second edition of Campbell's *Operative Orthopedics*, report the use of homogenous bank bone in 30 patients Grafts were used for internal fixation, fillage and massive grafts, and spinal fusions Time of observation did not permit final conclusions

One of the authors (L.F.B.) has used frozen homogenous bone in 39 operations from 55 donors at the Geisinger Memorial Hospital. The operations included.

Spinal fusions	22
Onlay bone grafts	10
Bone cysts	4
Arthrodesis of wrist	1
Osteotomy of femur	2

There was one wound infection following spinal fusion in which only a few chips were extruded and complete fusion eventually resulted. Two onlay grafts refractured, probably because of too early weight-bearing. Added precautions or longer periods of immobilization are now employed for all patients in whom the massive onlay grafts are used.

The use of bank bone at the New York Orthopaedic Hospital is shown in the following table Refrigeration at 2° to 5°C was employed earlier and was superseded by the freezing method in 1946.

TABLE II

USE OF BONE BANK IN 223 OPERATIONS

(NEW YORK ORTHOPAEDIC HOSPITAL)

	Refrigeration 2° to 5°C.	*Freezing −25°C.*
Total patients	25	162
Total donors	33	203
Total patients' operations	30	193
Operations		
Spine fusions		
scoliosis	22	118*
lumbosacral	1	22
repair pseudarthrosis	1	15
tuberculosis		16
Miscellaneous (Fracture, hemivertebra, osteo-arthritis, adolescent kyphosis)		7
Bone cysts and osteitis fibrosa		1
Enchondroma		1
Epiphysiodesis		1
Fibrous dysplasia	1	2
Osteotomy		2
Arthrodesis, wrist		2
Repair pseudarthrosis		1
Ununited fractures	2	2
in osteogenesis imperfecta	3†	
Complications		
Infections		2
Fracture of onlay graft	1	
Failure of soft tissue coverage	1	

* 45 autogenous transplantations, 73 homogenous transplantations

† Smith's operations: 1930, 1933, 1942

A review by J. P Miller in 1948, of New York Orthopaedic Hospital patients in whom frozen homogenous bone was used, disclosed that only 36 of the 73 scoliotic patients fused by this method had been followed long enough for adequate evaluation. In this series there were eight pseudarthroses, equivalent to an incidence of 22.2 per cent The 22 lumbosacral fusions were incompletely studied, since some of them had not been observed long enough to permit the taking of valid flexion and extension films. Suffice it to say, however, that in a review of 8 of these cases, 6 pseudarthroses were discovered, 4 being in the

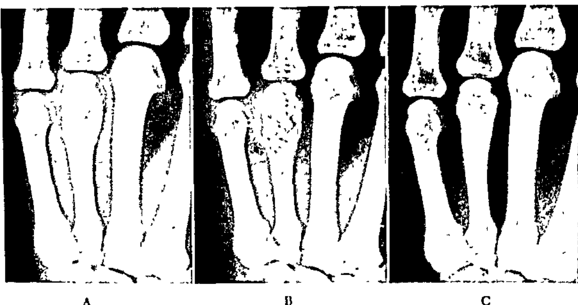


Fig. 9 –(A) Enchondroma of fourth metacarpal head, female, age 29 (B) Twenty-eight days after operation of curetting and packing with homogenous spinal bone chips which had been preserved 17 days at −25° C (C) Fifteen months after operation, excellent repair.

L4-L5 region, and 2 being in the L5-S1 region In the operations for the repair of pseudarthrosis of the spine there were 11 cases. There were 4 failures in this series, equivalent to an incidence of 36 3 per cent All low backs had early ambulation with screw fixation Patients with a failure of spinal fusion as demonstrated by flexion and extension roentgenograms did not necessarily manifest failure of fusion clinically, making for some confusion, since a similar study of flexion and extension views before the period of bank bone had not been made. The end results of the fusion for tuberculosis are not reported, owing to insufficient duration of follow-up which in our estimation should be at least two years In the remaining types of cases, there have been no failures.

In attempting to evaluate the end results of grafting procedures in which stored bone has been used, it is important to realize that in almost every case there has been a combination of both preserved bank bone and immediate autogenous bone taken from the local operative area, the Hibbs type of spinal fusion being reinforced with bank bone Another variable in almost every case is the relative amount of each of these types of bones, an estimation of which only the operator is capable, and that to a limited degree For the above reasons, it is impossible to make any definite statements as to which of the various

were less successful Weaver's conclusions, in an honest evaluation of his results, coincides with the writers', in that frozen homogenous bone has a definite place in orthopedic surgery but it also has its limitations.

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* 45 autogenous transplantations, 73 homogenous transplantations
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COMPLICATIONS

The complications encountered in the various series of operative procedures compare favorably with those of a similar series of operations in which autogenous transplants were used. Such important factors as the status of the recipient bone, pre-existent infection, soft tissue coverage, and the local blood supply play parts in the success of any transplant. The failure of massive onlay cortical transplants is apparently due to the longer period required for these transplants to become a living part of the host. Such transplants should be protected for a longer period than normally expected for autogenous transplants.



FIG. 11.—Spinal fusion chip of homogenous iliac bone, preserved preoperatively 11 days at −25° C., recovered for study 126 days following transplantation. Male, aged 12; necrosis and partial erosion of transplant; considerable appositional immature bone present.

EVALUATION

The feeling at present is that the bone bank has a definite place in an institution which is doing a large amount of elective orthopedic surgery. Stored bone is useful in those patients whose condition does not warrant an extra operation for the removal of autogenous bone, and in patients, particularly scoliotics, from whom sufficient bone can be removed at a first stage operation for use in that stage and in subsequent stages, the bone being stored in the bank in the interim. In the evaluation of our own end results clinically, we have seen no appreciable change in the incidence of pseudarthrosis when compared with similar cases in which more conventional methods of transplantation were used. Finally, it is our opinion that bank bone, homogenous or autogenous, should be regarded as a substitute and is not to be considered as efficient as the immediate autogenous transplant.

elements has been responsible for the success or failure of any given case Similarly we are unable to make any accurate comparison, clinically, between stored bone and other types. In our clinical series there are just 4 instances of pure homogenous transplantation of stored bone. Only homogenous bone preserved by freezing was used in one case each of enchondroma of the finger, osteitis fibrosa of the fibula, bone cyst of the tibia, and fibrous dysplasia of the ulna. That this type of bone was utilized effectively is shown by the follow-up roentgenograms (Figs. 9 and 10). For comparison there are 2 cases of bone



FIG 10—(A) Osteitis fibrosa of the fibula, with giant cells and old hemorrhage in a female aged 6 (B) Four days after operation of curretting and packing with homogenous iliac bone chips which had been preserved 42 days at −25°C (C) One hundred and forty days after operation. (D) One year after operation, excellent repair

cyst in which fresh syngenetic bone was transplanted directly from the parent donors with excellent results, and a case of giant cell tumor in which there was recurrence following direct transplantation of fresh syngenetic bone. In these few cases one could not ascertain that there was a difference in the relative behavior of the fresh syngenetic and the frozen homogenous transplants. Histologic examination of our few recovered spinal fusion chips of homogenous bone which had been stored by the freezing method showed necrosis of the transplant, appositional new bone formation (Fig. 11), and creeping substitution, a picture similar to that given by direct homogenous transplants and by homogenous transplants which had been stored in an ordinary refrigerator.

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The Normal and Abnormal Response of Bone Tissue



The Normal and Abnormal Response of Bone Tissue*

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INTRODUCTION

A DISCUSSION of all aspects of bone physiology, aside from its length, would be difficult to prepare because of the many disagreements among investigators. Our present knowledge of this subject is solidly secured in some fields, open to debate in some, and completely lacking in others. The present discussion will concern some pertinent features of bone growth, nutrition, regeneration, and infection in the light of present knowledge.

Besides providing structure and support for the body, the skeletal system plays an important role in the chemistry of the body. The metabolism of calcium and phosphorus is closely identified with that of bone. Protein forms a major part of osseous tissue. So many factors are known to play a part in the growth and development of the bones, that it is difficult to understand the function of each of them.

It is known that amino acids, glycogen, minerals (particularly calcium and phosphorus), many of the vitamins, and nearly all of the hormones play some definite role in the development and maintenance of bone. To understand the mechanisms involved in normal bone formation, it has been necessary to study abnormal bone formation The study of pathologic processes has often aided in the understanding of normal processes.

That there may be actual congenital chemical abnormalities, just as there are congenital physical abnormalities, is a factor which may have been overlooked in the past Examples of chemical abnormalities which may occur in the body are. vitamin-D-resistant rickets and pseudohypoparathyroidism. In pseudohypoparathyroidism, it is thought that the disturbance, which is similar in character to hypoparathyroidism, is due not to a lack of the hormone but to an inability to respond to it (Albright and Reifenstein).

STRUCTURE AND COMPOSITION OF BONE

A long bone is composed of a diaphysis or shaft, within which is the medullary cavity. Diaphyseal bone is compact. Here the haversian systems are closely

* A report based on a critical review of published research, 1940–1948.

the proximal epiphysis closes first, and here the nitrogen content is lower than it is at the distal epiphysis. The lowest nitrogen content area in both radius and ulna is to be found in the same anatomic cross section. Almost identical values in both bones are to be found as one progresses distally, because both radius and ulna have the same rate of growth at the distal epiphysis. Progressing proximally, the same is true if one takes into consideration the variation in the growth of each bone in the proximal direction The olecranon process produces the discrepancy.

They conclude that newly ossified bone has a fairly constant nitrogen content, which tends to show a gradual decrease as the bone matures. In other words, the older the part of the bone, and the older the bone, the greater the ash content, within certain definite limits The nitrogen content in the region of tuberosities is slightly decreased This they believe may be explained by the fact that muscles attach in these areas.

Bone development occurs by intramembranous ossification or by cartilaginous ossification Intramembranous bone arises directly from the mesenchymal cells. The development is most suitably studied in the flat bones of the skull. Here mesenchymal cells differentiate, osteoblasts appear, and the interstitial substance which is formed acquires the property of being calcified (Maximov and Bloom).

Intracartilaginous ossification occurs in the greater part of the skeleton Most bones are preformed in hyaline cartilage. The early cartilage models resemble, to some extent, the form and structure of future bones. Periosteum may develop as a tube around the cartilage model. The hyaline cartilage within undergoes degenerative changes and disappears It is replaced by bone.

The process begins with enlargement of the cartilage cells The matrix adjacent to the enlarged cells is calcified. Blood capillaries and mesenchymal cells enter the distended cartilage capsules. The mesenchymal cells in contact with the cartilage matrix become a layer of osteoblasts Osteoid develops on the calcified matrix. The preformed cartilage model is thus invaded and transformed to a bony model with marrow spaces, compact diaphysis, and cancellous metaphysis.

BONE GROWTH

John Hunter in his investigation on bone growth in the middle of the 18th century implanted metal pellets in the shafts of long bones and concluded that linear growth occurred only at the epiphyses. He thus founded the modern concept of bone growth.

At the bone ends, growth in length occurs by a process similar to that already described The cartilage cells proliferate, align themselves in columns, degenerate, and are invaded. The intercolumnar matrix is calcified, and osteoid tissue is laid down upon the spicules

When the epiphyses appear, a cartilaginous plate, the epiphyseal plate, remains between epiphysis and diaphysis. It is this plate which plays such an important part in the future longitudinal growth of the bone. When growth is complete this plate is replaced by bone.

There are at least three sources of evidence which indicate that linear growth

packed, with intermediary systems filling in to form a solid supporting mass (Maximov and Bloom).

The epiphyseal areas are composed of spongy or cancellous bone. Definite systematic arrangement in spongy bone is not always discernible Here the trabeculae are loosely interwoven in irregular bony spicules.

Both spongy and compact bone are being continuously remodeled. The remodeling is most active during growth and continues even after full growth has been reached, but at a slower rate. It has been shown that in 50 days, 29 per cent of epiphyseal mineral elements, and about 8 per cent of diaphyseal have been replaced (Hevesy et al.)

The haversian system may be considered as the basic structural unit of bone.

TABLE I

NITROGEN CONTENT OF BONE (IN GM PER CENT)

Animal	*Calf*	*Steer*	*Cow*	*Bull*
Age	4 weeks	2 years	3 years	5 years
Area near proximal epiphysis of radius	5 32* Epiphysis open	4 74†	4 64†	4 43†
Center of diaphysis of radius	4 24	3 70	3 74	3 50
Area near distal epiphysis of radius	5 37*	5 25*	4 86†	4 76†

* Epiphysis still open.
† Epiphysis closed

It comprises a central canal surrounded by lamellae composed of a hard interstitial substance

In the lamellae are lacunae containing osteocytes. Small canaliculi communicate with the lacunae and the central canal These canaliculi probably serve to maintain bone nutrition.

The hard interstitial substance is composed of protein, minerals, and water. Osteocollagenous fibers, running in different directions in different lamellae (usually perpendicular to each other in alternating lamellae) are united by a binding substance in which the calcium salts are deposited (Ruth). Calcium and phosphorus comprise the greater part of the ash content of bones.

Strobino and Farr have studied the variation of the ash and nitrogen content of bones Their studies have led them to conclude that there is a definite pattern in the relationship of ash to nitrogen, particularly in the shafts of the long bones. They believe that the nitrogen content bears a direct relationship to the age of the animal

In Table I the nitrogen of diaphyseal bone shows a decline as the age of the animal increases Conversely, the ash content shows an increase.

Strobino and Farr point out further that in the mid-portion of the radius, where *the center of ossification was to be found, the nitrogen content is* always the lowest. As one approaches the epiphysis the content increases In the radius

retarded in long bones than linear growth (Phemister, 1935). Armstrong severed portions of the brachial plexus in rats and noted that appositional growth was reduced more than epiphyseal growth.

In bone growth and regeneration three elements are involved; the cells, the organic matrix, and the mineral salts. The role of the osteoblast has been variously interpreted To one group of workers this cell is a connective tissue variant without any specific bone-forming property Leriche believes bone formation requires only the creation of an ossifiable connective tissue medium and the setting free of inorganic salts in the vicinity of this medium. Such a process requires a proliferating tissue of an embryonal type, provided in growing bone by vascularization and resorption of the cartilage, and in healing bone by the organization of a clot. The osteoblast according to this theory is a connective tissue cell, swollen as a result of its incorporation in a bone forming medium. This theory accepts the conception of osteoblasts playing a part in the production of phosphatase which, when acting on complex organic phosphorus, releases phosphate ions leading to precipitation of calcium phosphate in the osteoid or ossifiable medium.

More recently most investigators have found the osteoblast plays a more active part in bone formation. They assign to the osteoblast the ability to form osteoid tissue, as well as recognizing its importance in the production of phosphatase Experimentally, both periosteum and endosteum will form bone *in vitro* while a culture of simple fibroblasts never forms bone. In humans with osteogenic sarcoma, the metastasizing osteoblast shows a marked inclination to form osteoid and bone in its new site.

New bone formation occurs only in newly formed undifferentiated connective tissue. It will not occur in fully differentiated tissue. Urist and McLean have shown that the newly formed osteoid tissue readily accepts salts, and that a stage of osteoid refractory to mineral salts is not physiologically typical of bone formation Under certain abnormal conditions such as rickets, the osteoid stage is marked In human growth osteoid is only occasionally encountered, but in fractures this stage may be more prominent.

The mineral content in the case of growing bone is probably borne to the site of production by humoral means In regeneration of bone following fractures, or in transplantation of bone, there is also a local transfer from adjacent hyperemic bone and perhaps from nearby necrotic fragments The stimulus for deposition of the precipitate may be dependent upon enzyme action through which the fluid in relation to the area of cellular activity becomes highly supersaturated with calcium phosphate A principal actor in this enzyme reaction is phosphatase, acting on a substrate of various phosphoric esters. In addition to the osteoblast, proliferating cartilage cells and the cells of the osteogenetic layer of the periosteum produce this enzyme.

The process by which bone is resorbed is not clear. As stated above, the resorption of bone is an integral part of bone growth and the formation of bone shape The role of the osteoclast in resorption of bone has been challenged and its presence in the vicinity of resorption is considered sequential. Decalcification probably never occurs (O'Brien and Morgareidge, McLean). When bone is resorbed, it is removed *in toto,* mineral content and organic matter are simultaneously removed (O'Brien and Morgareidge).

occurs only at the ends of long bones The employment of artificial markers in the shaft has repeatedly corroborated Hunter's original experiments. The feeding of madder to experimental animals and later noting the distribution of the dye in newly formed bone has resulted in similar conclusions (Payton; Brash). Lastly, use has been made of the lines of increased density, often seen in growing bone, by observing and measuring the migration of these lines by roentgenograms (Brash).

Madderization of experimental animals has shown also, that increase in length results primarily from new bone formed between the disk of growth cartilage *and the metaphysis, and that linear increase from the epiphysis itself is not* significant. Increments of length are unequal at both ends of long bones. The greater increment occurs at adjacent ends of the tibia and femur and at the remote ends of the radius and humerus (Payton).

Payton and Siegling have shown that the epiphysis does not grow at its junction with the cartilage plate. This area is inactive. Actual growth of the epiphysis occurs beneath the articular cartilage adjacent to epiphyseal bone. Here a sluggish type of enchondral bone formation occurs with the basal layer of swollen hyaline cartilage cells of the articular cartilage forming rows and being replaced by bone.

Circumferential growth is always intramembranous (Brash). New deposits of bone are constantly being added from the periosteal cells lining the cortex by a process of accretion This process provides an explanation for increased circumference of a shaft but provides no answer to explain growth of the marrow. If this accretion were not accompanied by a resorptive process on the inner side of the shaft, all growth in the transverse diameter would be represented by cortical bone with the marrow occupying a fixed area throughout life.

This absorption of bone accomplishes another purpose. It is probably responsible for the shaping of bones and gives them their individual anatomic configurations. Brash has termed this process "modeling absorption" and it occurs on all bone surfaces, both of enchondral and intramembranous origin. Modeling occurs rapidly during growth and slowly in the adult.

An excellent example of this modeling process may be seen in any long bone. The epiphyseal cartilaginous disk is located in the flared end of the bone. The new bone formed from the cartilage plate is wider than diaphyseal bone. Such bone in the course of its migration into the narrower diaphysis must lose girth and it does so by absorption and accretion. In some forms of dyschondroplasia the terminal flare of a long bone is lost owing to the failure of modeling. Experimental evidence indicates that vitamin A plays a role in the remodeling process independent of its action on the linear growth of bone, but apparently related to cartilage cell cytomorphosis (Wolbach, 1934).

Growth in membranous bone is by surface accretion together with an absorptive process which gives shape. The radius of curvature of the bones of the cranial vault continually changes during growth by virtue of such surface changes and allows an increasing cranial capacity.

Clinical experience suggests that enchondral ossification, which phylogenetically precedes intramembranous ossification, is more resistant to environmental vicissitudes than the intramembranous type. In poliomyelitis, *Still's disease*, or bone atrophy resulting from other causes, circumferential growth is more severely

erate. Degeneration of the mature cells proceeds to a certain extent. The matrix is densely calcified for the depth of a few cells, and eventually a thin bony plate is formed across the surface of the epiphyseal disk on the metaphyseal side.

The Role of Calcium in Bone Nutrition

Calcium is one of the essential body minerals Practically all of it is to be found in the skeleton (Pecher). The abnormal reduction of calcium in the diet will retard growth and lead to a voluntary decrease in food consumption (Boelter and Greenberg). A low-calcium rickets will result. The bones are light in weight, and the calcium content is diminished.

Restoring calcium to the diet will help to restore the health of the animal.

The Role of Phosphorus in Bone Nutrition

With a reduced intake of phosphorus a similar condition is noted. In this case a low-phosphorus rickets develops, even though vitamin D and calcium are given in amounts normally required (Follis et al.).

In rats on the phosphorus-restricted intake, most of the endocrine glands show some histologic evidence of atrophy.

The Role of the Vitamins

Three of the vitamins, namely A, C, and D, have been shown to affect bone directly Others may have an indirect effect The vitamins of the B-complex are thought to affect bone by the part they play in general nutrition. In these deficiencies the epiphyseal plate may be narrowed and bone changes occur which resemble the conditions found in inanition (Wolbach and Bessey).

The studies of Warkany et al have emphasized one significant feature They have been able to produce rats with congenital anomalies by feeding pregnant females a deficient diet. The deficient substance responsible for the anomalies is, he believes, riboflavin.

Baby rats were produced with such skeletal abnormalities as short mandibles, fused ribs, shortening or complete absence of the radius, ulna, tibia, fibula, metacarpals, and phalanges. The malformations were shown to date back to the cartilaginous or precartilaginous stage of the structure affected. Defects of ossification were secondary to cartilaginous deformities, endochondral ossification was frequently delayed and faulty

The bones most commonly affected are indicated in Table II.

TABLE II

Frequency of Osseous Defects in 100 Cleared Abnormal Specimens

Bone	Frequency	Bone	Frequency
Tibia	93	Ulna	50
Mandible	80	Humerus	34
Ribs	75	Hindfoot	31
Fibula	63	Maxilla	8
Radius	58	Scapula	6
Hand	54	Clavicle	6
Sternum	52	Femur	1

Vitamin A In vitamin A deficiency, the most obvious bone changes occur in the young (Wolbach). The epiphyseal disk becomes thinner as the cartilage

The problem of bone growth and regeneration is complex, involving not only an increase in size but also alteration of form. The directing influences of such features of bone growth are not understood. Heredity and mechanical and endocrine factors have all been implicated. Fell and Robison demonstrated the inherent capacity for bone to grow and differentiate without endocrine or mechanical direction. Femurs of six-day-old embryonic chicks were grown *in vitro* in embryonic extract and plasma. Although the transplanted specimen was a rod of cartilage capped with an anlage of head and condyles, after three to 27 days of incubation, growth and differentiation had occurred and the normal femoral configuration was approached.

Lacroix has demonstrated experimentally the presence of a humoral substance in growth cartilage which when extracted in alcohol and injected in muscle produced a large osteoma together with all the components of growing bone. His work would seem to prove that not only the organization and orientation of the skeleton but also osteogenesis itself is under the influence of such an organizer which may be elaborated by the growing cartilage cells.

NUTRITION

Dietary substances which produce changes in bone growth usually produce changes in other tissues as well. If the endocrine tissues are affected in the process, and they frequently are (Follis et al., Wolbach and Bessey) the final picture obtained may not represent a direct effect upon bone, but a superimposed effect produced by hormonal changes. There are many aspects to the problem of bone nutrition that have yet to be worked out.

All vitamin deficiencies that result in severe malnutrition (and this includes most of them) arrest growth of bone. Malnutrition resulting from inadequate amounts of a perfect diet also arrests bone growth Rats fed on a 50 per cent restricted caloric intake fail in their general growth and show a complete cessation of skeletal growth as well (Handler et al)

In general, young animals are affected to a greater degree than older animals. Skeletal growth is roughly proportional to general body growth In older animals, while skeletal changes most definitely do occur, the most obvious feature is their loss of weight

Animals fed on a diet which is inadequate because it lacks an essential amino acid voluntarily tend to reduce their food intake, even though ample amounts *of all other substances are supplied (Harris et al).*

The effects of these dietary disturbances are always to be noted in bone, particularly in the region of the epiphysis, if growth has not stopped. The histologic picture may vary, depending on several factors, among which are: (1) the degree of the deficiency, (2) the duration of the deficiency, (3) the age of the animal (Silberberg and Silberberg).

The changes to be noted in the bones are the following. (1) the cortices are thinner than normal, (2) there are fewer bone trabeculae present, (3) the osteoblasts appear to be smaller and atrophic, (4) there is no excess osteoid; (5) there is a decrease in the width of the epiphyseal plate.

The cartilaginous plate becomes decreasingly active. The cells do not prolif-

It is in this area, at the junction of the diaphysis and epiphysis, that the bone is weakened. Fractures in this zone are to be frequently seen in severe cases of scurvy. Then too, because of the failure of formation and maintenance of intercellular substance, the periosteum may pull away from the outer bony surface.

That part of the bone which is laid down before the onset of scurvy is less affected than that part which develops subsequently (Ham and Elliot).

In the adult bone, changes in the form of osteoporosis become manifest. Osteoclastic action continues while there is interference with osteoblastic action.

Vitamin D. Vitamin D deficiency in the young leads to rickets. The histopathologic picture has been described (Freeman and McLean) At the epiphyseal plate the following changes are noticed. the cartilage matrix fails to calcify; the resorption of the degenerating cartilage cells is retarded and irregular; there is apparent widening of the plate, the cell columns are irregularly arranged; osteoid tissue is laid down but it fails to calcify, or it calcifies only in part, depending upon the degree of the deficiency.

Because the osteoid is not readily resorbed, the bone is not remodeled at the epiphyseal ends but continues to remain in the abnormal expanded state (Weinman and Schour). In the shafts, the deposition of osteoid proceeds appositionally and the cortices may thicken Osteoclastic action occurs, providing that an osteoid border does not cover the normal bone systems and trabeculae.

The above changes are to be noted in rickets in the young or still growing animal. After the termination of growth, osteomalacia develops with vitamin D deficiency. In this condition the calcification of osteoid laid down in the normal process of remodeling is retarded.

The mechanism by which vitamin D affects the growth of bone is not entirely understood While it is generally believed that this vitamin aids in the absorption of calcium and phosphorus from the intestine, Greenberg believes that it also has some direct effect upon the deposition of these substances in the bones and Albright and Reifenstein believe that the kidney is involved in the mechanism in some way.

Hypervitaminosis D. With the administration of large doses of vitamin D, metastatic calcification involving many tissues may be found (Kaufman et al.). If the calcification occurs in the kidneys, renal function may be disturbed. The exact nature of the disorder is subject to discussion (Tumulty and Howard). It seems less likely that the condition results from actual toxicity of the drug rather than from the usual actions of vitamin D. It is believed that the tissue necrosis is the result of a calcium and phosphate precipitation in the tissues.

THE ENDOCRINES: THEIR INFLUENCE ON THE SKELETAL SYSTEM

In attempting to describe the influence of the endocrines upon the skeletal system no effort has been made to include a description of their general metabolic actions. It is understood that the bone changes which may be evident in endocrine disturbances are but a part of the total picture. However, those aspects of general endocrine physiology are not within the scope of this subject.

In the endocrine system the pituitary is the master gland. Not only does it control growth directly by its somatotropic hormone, but it also influences many

cells cease to divide. Eventually a thin bony plate is formed across the diaphyseal side of the epiphyseal cartilage. With the cessation of endochondral growth remodeling also stops, but appositional bone formation may continue in conformity with normal growth patterns.

The long bones of an A-deficient animal are shorter and thicker than normal. The shortening results from the failure of endochondral bone growth. The increased thickness is the result of continuation of appositional growth, and also of the failure of remodeling to occur near the epiphysis.

In some species, the skeletal growth stops before the growth rate of the animal as a whole. Wolbach believes that the central nervous system continues to grow in animals after the cranial cavity has ceased to enlarge. It is this discrepancy which leads to overcrowding, buckling, and herniation of the nerve roots, resulting in paralysis. Mellanby, on the other hand, has stated that the pressure on nerves is produced by continued irregular appositional bone growth.

When excessive doses of vitamin A are administered to young animals, there is an acceleration of growth processes in the bones. There is rapid consumption of the epiphyseal cartilage and in some species the epiphyses close prematurely. Normally the distal femoral epiphysis in guinea pigs will close in the 30th week. With excessive amounts of vitamin A it can be made to close in two or three weeks. There is a retardation of growth, and a decrease in food consumption. Remodeling of the bones, which is closely related to their growth, is greatly accelerated in some species. There is an increase in the number of osteoclasts as determined by the dosage of vitamin A. Remodeling may be so accelerated that fractures are easily produced. The occurrence of fractures is accounted for by the extensive loss of cortical bone before the newly formed osteoid has acquired sufficient firmness to withstand normal stresses and strains

Vitamin C With reference to bone, the fundamental disturbance in scurvy is the failure of normal osteoblastic activity (Wolbach and Bessey). Osteoid is either not produced, or it is produced in a defective form Man, monkeys, and guinea pigs are said to be the only animals unable to synthesize this vitamin

It is in the region of the epiphysis, where longitudinal growth of bone is occurring, that the effects are most obvious Here the cartilage cells continue their usual process of division, maturation, and degeneration. The cartilage matrix is calcified normally Blood vessels enter the degenerating cells. The zone of calcified cartilage matrix continues to widen but no osteoid is laid down in the area as it should be normally. One can only find capillaries and connective tissue cells.

[illegible] there is detritus, [illegible] issue cells about [illegible] piphyseal lesions are produced by the mechanical strains of movement, for immobilized extremities are without the usual micro-fractures and debris In these cases the true picture of scurvy is without the added effect of trauma. No osteoid or bone is found on the calcified cartilaginous lattice Myeloid elements are to be found in the lattice area. There is no proliferation of connective tissue cells, no fibrin-like material, and no hemorrhage present in the metaphyses of the legs of guinea pigs protected with plaster casts

considerable period. There is interference with the growth of cartilage. The epiphyseal plate becomes thinner. There is a decrease in the size and the number of cartilage cells. The matrix will become deeply calcified on the diaphyseal side, and bone trabeculae grow up to seal off the cartilage cells from invasion by blood capillaries. In this manner the epiphyseal plate is sealed off by either its own calcified cartilage or bone (Becks et al.).

Parathyroid Glands. The parathyroid glands secrete a hormone which has to do with calcium and phosphorus metabolism. As these elements make up the chief mineral constituents of bone, it is easily understood that disturbances of the secretion of this hormone can be reflected by changes in the skeleton.

The mechanisms by which the hormone acts have been debated for some time. Albright and Reifenstein believe that the chief mode of action is in some way related to the excretion of phosphate by the kidney. The changes in calcium metabolism are thought to follow and to be, more or less, dependent upon the phosphorus metabolism. The content of calcium and phosphorus in the serum is related to the reaction occurring at the bone surfaces where deposition and resorption of bone are constantly taking place. The other theory of action considers this hormone to act directly upon bone (Collip et al.). There is something to be said for both of these concepts (McLean).

Hypoparathyroidism: In this condition there is a failure of the parathyroid hormone production It may occur following thyroidectomy if the parathyroids are also removed. It has been reported in infants born to hyperparathyroid mothers. In some it may be idiopathic. The association of hypoparathyroidism and moniliasis has been described (Sutphin et al.).

There is usually a decrease in both serum calcium and phosphatase. The serum phosphorus is elevated.

The bone changes reported in this condition are not consistent (Emerson et al.; Drake et al) There is apparently no delay in the appearance of the ossification centers. However, there may be either an increased or a decreased bone density apparent on roentgenologic examination. The reason for this degree of variation is not easy to comprehend (Albright and Reifenstein).

Hyperparathyroidism: Hyperparathyroidism is the result of overproduction of the parathyroid hormone. All degrees of hyperfunctioning parathyroids are to be found The disturbance may be marked or mild.

Parathyroid hypertrophy is thought to be related in some way to the calcium intake Rats on a low calcium, high phosphorus diet tended to develop hypertrophy of the parathyroids. On a high calcium, low phosphorus regime they did not (Ham et al.). Apparently with a low serum calcium the glands overfunction in an attempt to restore the normal serum content of calcium. The only obvious source of stored calcium in the body is the skeleton (Pecher).

Associated with hyperparathyroidism is an elevated serum calcium and phosphatase and a decreased serum phosphorus.

Osteitis fibrosa cystica generalisata is the name given to the bone disease, which if present, accompanies hyperparathyroidism Von Recklinghausen's name was originally associated with the bone lesions. All variations of bone rarefaction are to be encountered, from the minimal to the most severe resorption of almost the entire skeleton. In the severe types compact bone may be replaced by spongy

of the other glands by specific trophic hormones, thyrotropic, gonadotropic, and adrenocorticotropic substances have been described.

The system is made more complex by the fact that the other glands secrete hormones which exert either stimulating or inhibitory influences upon the pituitary, and in some cases upon each other.

The failure of hormonal production may be complete or partial. The degree of the deficiency will determine the effect upon the structures affected. If, for example, the somatotropic hormone of the anterior pituitary is partially lacking, growth may be retarded. If it is completely lacking, growth will stop.

If there is a disturbance of but one endocrine structure, the changes produced may be readily understood. However, not infrequently there is a disturbance of more than one glandular structure. If two or more glands are involved the picture may not be clear-cut at all.

It is to be emphasized, too, that the changes which are apparent in bones will depend upon whether or not the epiphyses are closed or open, whether the individual is young or mature at the time of onset of the condition.

Anterior Pituitary. The anterior pituitary produces a hormone which stimulates the growth of the animal directly. In those conditions in which growth of the animal is affected by pituitary dysfunction, there may be over or underactivity of the eosinophilic cells.

Pituitary Gigantism: If overproduction of the growth hormone occurs while the epiphyses are still open, an increase in the general body size is to be noted. The growth hormone of the pituitary apparently stimulates the activity of the epiphyseal plate (Becks et al) and also it tends to keep the plate open for a longer period of time than normal. The condition is termed gigantism. In most of these cases a tumor of eosinophilic cells is to be found in the anterior pituitary (Selye).

The growth of the individual suffering from this abnormality is usually symmetrical and proportional, but this is not always the case. The cranial cavity, which enlarges as the brain enlarges, is not increased in size because the brain size is usually normal The bones of the face and base of the skull may, however, be enlarged

Acromegaly. If the growth stimulus should begin to act again after the epiphyses have closed, then, of course, an increased longitudinal growth of the bones is not possible, except to a limited degree. Appositional growth, however, can and does occur. The enlargement of the bones of the hands, feet, and face is probably the most obvious feature. The mandible becomes acutely prominent. The vertebral bodies are increased markedly in size. Here the new bone is laid down particularly on the anterior and anterolateral surfaces of the body, to give the appearance of a giant's vertebra.

Pituitary Dwarfism: The absence of the anterior pituitary growth factor will lead to dwarfism. The degree of dwarfism depends partly on the age of onset of the condition and partly on the degree of the deficiency. If, for example, complete failure of the growth hormone should develop at seven years of age, the child would remain at the height he had obtained at that age.

The age of appearance of the ossification centers is delayed. The growth of the skeleton is retarded. The epiphyses do not close but remain open for a

considerable period. There is interference with the growth of cartilage. The epiphyseal plate becomes thinner. There is a decrease in the size and the number of cartilage cells. The matrix will become deeply calcified on the diaphyseal side, and bone trabeculae grow up to seal off the cartilage cells from invasion by blood capillaries. In this manner the epiphyseal plate is sealed off by either its own calcified cartilage or bone (Becks et al.).

Parathyroid Glands. The parathyroid glands secrete a hormone which has to do with calcium and phosphorus metabolism. As these elements make up the chief mineral constituents of bone, it is easily understood that disturbances of the secretion of this hormone can be reflected by changes in the skeleton.

The mechanisms by which the hormone acts have been debated for some time. Albright and Reifenstein believe that the chief mode of action is in some way related to the excretion of phosphate by the kidney. The changes in calcium metabolism are thought to follow and to be, more or less, dependent upon the phosphorus metabolism. The content of calcium and phosphorus in the serum is related to the reaction occurring at the bone surfaces where deposition and resorption of bone are constantly taking place. The other theory of action considers this hormone to act directly upon bone (Collip et al.). There is something to be said for both of these concepts (McLean).

Hypoparathyroidism: In this condition there is a failure of the parathyroid hormone production. It may occur following thyroidectomy if the parathyroids are also removed. It has been reported in infants born to hyperparathyroid mothers. In some it may be idiopathic. The association of hypoparathyroidism and moniliasis has been described (Sutphin et al.).

There is usually a decrease in both serum calcium and phosphatase. The serum phosphorus is elevated.

The bone changes reported in this condition are not consistent (Emerson et al, Drake et al.) There is apparently no delay in the appearance of the ossification centers. However, there may be either an increased or a decreased bone density apparent on roentgenologic examination. The reason for this degree of variation is not easy to comprehend (*Albright and Reifenstein*).

Hyperparathyroidism: Hyperparathyroidism is the result of overproduction of the parathyroid hormone All degrees of hyperfunctioning parathyroids are to be found. The disturbance may be marked or mild.

Parathyroid hypertrophy is thought to be related in some way to the calcium intake. Rats on a low calcium, high phosphorus diet tended to develop hypertrophy of the parathyroids. On a high calcium, low phosphorus regime they did not (Ham et al.) Apparently with a low serum calcium the glands overfunction in an attempt to restore the normal serum content of calcium. The only obvious source of stored calcium in the body is the skeleton (Pecher).

Associated with hyperparathyroidism is an elevated serum calcium and phosphatase and a decreased serum phosphorus.

Osteitis fibrosa cystica generalisata is the name given to the bone disease, which if present, accompanies hyperparathyroidism. Von Recklinghausen's name was originally associated with the bone lesions All variations of bone rarefaction are to be encountered, from the minimal to the most severe resorption of almost the entire skeleton In the severe types compact bone may be replaced by spongy

bone. Newly formed bone may remain uncalcified. Osteoclasts are conspicuous by their numbers. The marrow becomes fibrous in character. Fractures occur frequently, but heal readily with poorly calcified callus. Distortions similar to those occurring in osteomalacia may develop. Cysts in the bones are common (Boyd).

Thyroid. General body growth is clearly related to the hormones produced by the hypophysis and thyroid. The pituitary gland, by the action of its thyrotropic hormone, governs to a certain extent the activity of the thyroid. The thyroid, in turn, is thought to influence the pituitary by its secretion. With the removal of the hypophysis, growth ceases. With the removal of the thyroid, growth is considerably retarded, but may be stimulated to a certain extent by pituitary growth hormone, with resulting increase in size but no advance in differentiation (Becks et al.).

Hypothyroidism. The disturbance of growth resulting from hypothyroidism will depend upon the age of onset of the condition. If, as in cretinism, there is a congenital absence of the thyroid hormone, dwarfism is the result. Growth is considerably retarded. The ossification centers are slow to appear. The bone age remains far behind the actual age Endochondral ossification occurs slowly, so that cartilage may be present in the bones for a long time. The epiphyseal plates remain open as they do in pituitary dwarfism and finally a thin layer of bone is laid across the diaphyseal surface of the plate, sealing it off. Appositional bone growth may continue, and therefore the bones are comparatively short for their width.

Should hypothyroidism, develop in childhood (childhood myxedema), the growth arrest is less obvious than it is in cretinism. It again depends upon the age of the individual at the time of onset. The delay in the appearance of ossification centers is a prominent feature. On roentgenographic examination the epiphyses may give the appearance of being fragmented, as if there were multiple foci of ossification. The bone density may be subnormal (Wilkins and Fleischmann).

Hyperthyroidism. This condition is apparently rare in children. The effects noted on the growth of the child may be either acceleration or inhibition, depending upon the severity of the condition (Selye).

In adults, hyperthyroidism occurs more frequently in females than in males. The age group is usually postmenopausal (fifth and sixth decades). Osteoporosis is a common finding, and pathologic fractures may occur (Williams and Morgan). There is a tendency in hyperthyroidism to a constant or intermittent loss of nitrogen, calcium, and phosphorus (Barr and Shorr). It is believed that the effect of the hormone on bones is not specific. The general catabolic process probably accounts for the osteoporosis (Albright and Reifenstein, Selye). The bone changes are not easily reversed after removal of the thyroid, but pain may completely disappear.

Testes and Ovaries The differences in the adult male and female skeletal structures have always formed the basis for the belief that the sex glands had something to do with bone development. Since the work of Keys and Potter when they observed hyperossification in the medullary cavities of the bones of

female pigeons it has been realized that the estrogens are in some way related to bone formation. Albright has shown that both androgens and estrogens influence the retention of calcium, phosphorus, and nitrogen.

The anterior pituitary through its gonadotropic hormones stimulates the maturation of the gonads. If there is pituitary failure the hormones normally produced by that gland would be absent or deficient, and as a result the gonads would fail to mature. The primary deficiency resulting in gonadal hormone failure, therefore, may be in the pituitary gland or in the gonads themselves.

Hypogonadism. Eunuchism, resulting from castration, in young individuals before the epiphyses have closed is associated with moderate gigantism (Gardner and Pfeiffer). The extremities are long. The hands and feet are narrow, with elongation of the fingers. The bone age is usually retarded. The epiphyseal cartilages continue their growth beyond the usual age. The skull grows according to the brain size and is not enlarged.

In the adult, particularly in the postmenopausal state, failure of ovarian function is thought to have a direct bearing upon the osteoporosis so frequently observed in the skeleton. Increased medullary (endosteal) bone can be produced in rats and mice by estrogen injection (Day and Follis; Gardner and Pfeiffer). This bone disappears when the hormone treatment is discontinued. The action is thought to occur by stimulation of the osteoblasts.

By administering estrogen (and androgens) to postmenopausal women with marked osteoporosis, the bone pain can be eliminated. While the symptoms were relieved, no definite changes in the bones had been noted roentgenologically until Sherman showed not only roentgenologic improvement but also histologic improvement in a case of Paget's disease with superimposed postmenopausal ovarian failure (Sherman). The bone sections made before treatment contrasted greatly with those made after therapy.

The trabeculae were thin and few in number on the first biopsy. After treatment, the number of trabeculae had increased and there was a large amount of osteoid tissue. The tibial cortex, which was penetrated by a needle on the original biopsy, had to be cut with an osteotome on the second occasion.

Albright, Smith, and Fraser express the opinion that if osteoporosis occurs in the postmenopausal state, the same condition should occur in females at the time of puberty in cases of ovarian agenesis. Individuals with this condition are short in stature. Bone age is retarded. In those cases with delayed closure of the epiphysis and osteoporosis, changes in the spine occur resembling "epiphysitis" (Del Castillo et al.).

Hypergonadism does occasionally occur. In children it may be associated with a granulosa-cell tumor in females, and a tumor of the cells of Leydig in males. In either case the bone age may be greatly increased. The individuals are usually small because of premature closure of the epiphyses (Selye).

Adrenal Cortex. In Cushing's syndrome, severe osteoporosis may occur. The osteoporosis may be so prominent in the vertebral column that the intervertebral disks tend to occupy more space than do the vertebral bodies. The primary defect is thought to be the failure of bone production by the osteoblasts. In children there is not only an osteoporosis, but also a failure of growth. Some

of these cases are due to a cancer of the adrenal cortex. Some are thought to be due to an overproduction of the adrenocorticotropic hormone by the pituitary (Perloff et al., Albright).

The adrenogenital syndrome is believed to be associated with an excessive production of the adrenal cortical hormone which has to do with the stimulation of tissue growth. Children with this condition tend to grow more rapidly in every way than do normal children. The bone age is markedly advanced, but as the epiphyses close early, the final height of the individual is usually normal or possibly shorter than normal (Albright and Reifenstein).

BONE INJURY

Fractures

The bulk of recent experiments show that the healing of a fracture is primarily a local phenomenon (Urist and McLean, Murray; Armstrong). Medical literature abounds with references purporting to show how therapy directed toward correcting deficiencies in chemical balance or improving the vigor of the host might hasten fracture healing. The results of feeding selected diets, vitamins, endocrines, and other drugs are reported extensively, and in experimental animals correlations have been made between fracture healing time and the presence or absence of some chemical. It may, however, be safely said that there is no experimentally proved chemical or dietary regime which hastens union in a normal animal on an adequate diet. The importance of the surgical methods of reduction and immobilization is yet to be challenged.

Changes in the body metabolism do occur following a fracture. After fracture, there follows an initial period of metabolic depression, later metabolism increases to rise above the normal This period is characterized by an increased basal consumption of oxygen and an elevation of temperature. There is also found at this time a rise in urinary nitrogen with the maximum output occurring between the fourth and eighth day following fracture. After this period the excretion of nitrogen gradually declines. Cuthbertson believed that immobilization augmented this nitrogen loss but was not the sole cause of it He tried to correct nitrogen imbalance by high protein feedings but was only partially successful, the nitrogen output being diminished but not halted. This loss of endogenous protein has been fully confirmed in patients recovering from fractures

The lost nitrogen is thought to result from a general acceleration of the body metabolism with a smaller amount originating from the products of autolysis at the site of injury. This generalized nitrogen loss is not restricted to fractures but occurs after any injury and also in debilitated patients. During the healing of a fracture no changes have been noted in the blood serum level of calcium or phosphorus (Urist)

Bone growth occurs by ossification of tissue preformed in cartilage and more directly by ossification of undifferentiated connective tissue. The healing fracture repairs by both enchondral and intramembranous ossification.

At the time of fracture, blood from injured vessels of the marrow, periosteum, and surrounding soft tissue extravasates and forms a hematoma centered about

the fracture site. The ensuing clot contains all the formed elements of blood together with bone and muscle fragments. Organization of this hematoma begins within a few hours, but the hematoma may be so massive in fractures of the long bones that 30 to 60 days or longer may be required before such organization reaches the hematoma core (Urist and Johnson).

Swenson investigated some features of the hematoma in dogs. Immediately after fracture there was a shift of the pH to the acid side and values as low as 6.9 were reached in the 24 hour hematoma. In the course of 10 days there was a gradual reversal toward the alkaline side, the highest reading having reached 7.6.

The phosphorus value of the hematoma fluid showed a marked initial rise during the first 48 hours, reaching a peak of 18.7 mg. per 100 cc. of hematoma fluid (3-4 mg. in the blood serum). After 48 hours this value fell to the normal blood level but rose again on the seventh to 10th day to about 7.4 mg.

The hematoma alkaline phosphatase remained at blood level until the seventh to 15th day when it showed elevations as high as 56 Bodansky units. It thus appeared that the alkaline phosphatase activity awaited the alkaline shift, at which time a similar increase in the inorganic phosphorus values was noted. Swenson concluded that the increased phosphate ion results from a complicated enzymatic process involving phosphatase. This work conflicts with the views of Sterling and Murray who believed that the high local acidity at the fracture site produced an ideal medium for an increase in calcium and that later changes to alkalinity in the hematoma caused precipitation of the calcium phosphates.

Dallemagne noted a calcium loss in both segments of the broken bone in rabbits. This skeletal demineralization stopped long before the calcification of the callus was completed. The callus, therefore, must obtain much of its mineral from other sources.

The entire hematoma eventually is replaced by a fibrous type of connective tissue. That portion of the organized hematoma which lies between the fractured ends may secondarily differentiate into hyaline or fibrocartilage. It is thought that pressure and tension stresses as well as the original trauma favor chondrogenesis. Children will usually show a propensity to create more cartilage than adults. The connective tissue, hyaline cartilage, and fibrocartilage replacing the hematoma are known as procallus.

Cartilage may be present as islands in the center of the procallus. Many of these islands may coalesce to form an intervening cartilage disk between the fractured fragments.

The extent of cellular death adjacent to the fracture line was investigated by Ainsworth and Wright. A variable amount of cortex on both sides of the fracture gap lost its cellular structure. The endosteum of the haversian canals and the vessels also were destroyed. This necrotic area gradually blended with viable bone at a distance from the fracture. The highly cellular marrow showed a more limited necrosis. The cause of this tissue destruction is most likely due to a local circulatory deficiency.

Urist and Johnson also observed this necrosis in fractures in humans. They found that cortical death extended about 1 cm. from the fracture gap. In addition these studies revealed rarefaction of bone bordering the necrotic bone and principally involving the inner surface of the cortical bones. This was a later

manifestation and perhaps due to the hyperemia of actively proliferating tissue.

As the organization of the hematoma progresses, the first appearance of new bone is noted. In fractures of cortical bone this new ossification arises at a distance from the fracture just beneath the periosteum. The picture is that of intramembranous bone formation. The new bone spicules are bordered by large osteoblastic type of cells perhaps derived from the cambium layer of the periosteum. The new bone forms a collar about the cortex and then develops in the direction of the fracture. The invasion and replacement of the connective tissue progress in an organized manner. New bone appears only on the advancing front of the bone. No islands or separate nuclei of bone production are noted. At the active ossification zone many new vessels make inroads on the connective tissue and deposit bone tissue in their wake. Such bone tissue will usually have a border of osteoid tissue which will receive its charge of minerals at a later date.

The speculations regarding the relationships of osteoid matrix and bone have been answered by Urist and McLean. Working with rats, they showed that new osseous tissue can receive its mineral component as soon as it is laid down under optimal conditions. In rats no osteoid is seen unless there is a mineral deficiency such as occurs in rickets.

Working with fractures in humans, Urist and Johnson noted a narrow osteoid border on the new bone indicating a lag in the transport of minerals. As the healing accelerates in the later stages this failure of the minerals to keep the pace set by the cellular components becomes greater, and wider osteoid borders are found Bone production under conditions of normal growth shows little free osteoid. The definite lag seen in an adult fracture may be a result of the diminished circulating phosphorus in adults in contrast to the higher values seen in young children.

When the advancing osteogenetic front comes into contact with the cartilaginous elements of the procallus, most of which is in the neighborhood of the fracture gap, the enchondral type of ossification is observed. The swelling of the chondrocytes indicates their maturity and is similar to the changes seen in cartilage during growth at the epiphysis. There may or may not be a preliminary calcification of the cartilage matrix prior to the ingrowth of vessels and resorption of the cartilage.

The structure of the bone callus shows early differentiation. The bridge of bone *enclosing the segments of the shaft and the fracture becomes more compact* on its inner border and remains more spongy on its outer border.

Fractures through metaphyseal bone are somewhat less complicated. The external bone bridge is not a prominent feature unless there is wide displacement. Bone production replaces the connective tissue and cartilage, but this process commences from a wide base in the endosteum as well as the periosteum of the fractured segment.

The necrotic section of the shaft is invaded and replaced as new vessels enter the area. The role of the osteoclast in this process is not clear. Apparently it does not phagocytose the bone salt or the organic matrix (McLean). Moreover, halisteresis with salt being removed from the matrix probably does not

occur. Much doubt has been cast upon the idea of decalcification. The matrix and minerals are removed simultaneously in a way not yet understood.

The mineral supply of the callus is predominantly humoral in origin, with some added increment from transfer of shaft minerals to callus from resorbed or perhaps from necrotic bone. This increment is provided only late in fracture healing. The ability of rachitic rats to develop some calcium in the callus without corresponding calcification of the growing rachitic metaphysis indicates the probability of a local transfer of calcium (Urist).

Goisman and Compere demonstrated in animals that atrophic bone united as readily as normal controls. The atrophy was produced by a calcium-deficient diet and was determined by roentgenography. Before atrophy is shown on the film about 20 per cent of the minerals must be lost.

The disposition, shape, and size of the external bridge of callus in long bones follows a purposeful pattern. Bick has studied the callus pattern and has shown that it develops in response to compressive forces acting on the bone in such a way as best to transmit these forces from one fractured segment to the other. In general, the volume of the callus is in proportion to the degree of displacement of the fracture. Without displacement there is no alteration in the lines of force and the external callus in such an instance would be minimal. The external mass is not structurally an essential part of the final union. When the cartilage disk in the fracture gap is finally ossified, the external ossific mass is modified in accordance with function.

The hyperemia of bone in proximity to the fracture site mentioned above is responsible also for the overgrowth seen after fractures of the long bones in children. Compere and Adams have studied this problem and have shown that gross trauma over a considerable portion of the shaft with resultant widespread hyperemia may stimulate an epiphysis to longitudinal overgrowth. These studies have shown that the increased growth continues only during the healing period. They disclaim the idea that the growth represents a compensatory phenomenon from shortening resulting from the fracture.

Aseptic Necrosis

Bone may undergo necrosis independent of infection, as a result of several types of injury Loss of its blood supply, excessive pressure, or toxic influences are a few of the conditions which may cause such necrosis of bone. Little is known regarding the response of bone to pressure. Each bone in the organism is subject to many diverse pressures from muscle tone, muscle exertion, and gravity. It is recognized that excessive pressures do cause necrosis, but there is a paucity of experimental work on this phase of necrosis. Similarly the influence of noxious agents has been inadequately investigated.

The investigations of Phemister on necrosis due to vascular impairment have given an insight into this type of bone death with its subsequent regeneration. There is a variety of orthopedic conditions which are attributed to vascular impairment of bone. The most obvious are those instances of massive necrosis of large segments of a bone, such as the femoral head, after fracture or dislocation. Large free fragments of necrotic bone stripped of its soft tissue vascular bridge

are seen in fractures of the long bones. In children epiphyses may undergo necrosis The resulting changes as seen on roentgenograms are given a variety of names depending on the epiphysis involved. The initiating agent in this group is not known but may be a result of trauma. Most of the secondary and some of the primary ossification centers can develop such changes.

The principal pathologic changes in chronic hypertrophic arthritis have been noted in the cartilage, but changes in the underlying bone may precede the cartilage pathology Occlusion or sclerosis of the terminal vessels supplying the subchondral bone may represent the initial change, the subsequent more obvious cartilaginous pathology being secondary. Repeated minimal trauma may be an ancillary factor Small amounts of necrotic subchondral bone are occasionally found on microscopic section (Phemister, 1940).

Osteochondritis dissecans is another example of aseptic necrosis. An injury of a terminal vessel may be the instigating factor in this disease. Microscopic evidence indicates that the necrosis of bone antedates the cartilage separation. If the necrotic fragment remains firmly in its bed for a long interval, regeneration characteristic of aseptic necrosis is seen to occur (Phemister, 1940).

Caisson disease is an example of a disseminated necrosis often occurring in the region of terminal vessels and resulting from the release of nitrogen bubbles into the circulation or the tissue. Whether these bubbles act as emboli or whether the bone is destroyed by direct compression or pressure on vessels from nitrogen pockets in bone tissue is not yet clear (Kahlstrom et al.). The infarcted areas in the shafts of the long bones cause little disability and may remain or disappear The necrosis bordering the joints occurs in cancellous bone with a thin cortical covering and results in a collapse of trabeculae, causing secondary changes in the joint cartilage which may be irreversible. In such instances disability is pronounced.

Elderly individuals will occasionally show an irregular blotchy area of increased bone density representing necrotic bone due to embolism or occlusion (Phemister, 1940).

Jaffe and Pomeranz investigated bone from limbs amputated because of circulatory insufficiency and compared it with bone from normal limbs. They noted that the cells of the deeply situated lamellae of cortical bone normally die as part of the aging process This necrosis of the cells of the deep lamellae was more marked in the gangrenous limbs Here there is a more diffuse, insidious type of necrosis which casts no abnormal roentgenographic shadow.

Bone is more prone to vascular accidents than most tissue of mesodermal origin because of its limited vessel anastomosis. Blood is circulated through bone from three sources The nutrient artery dividing into ascending and descending branches is the single largest vessel. In the metaphyseal area numerous small vessels penetrate the cortex while periosteal vessels of small caliber enter the shaft throughout its length Bone owes its susceptibility to vascular derangements, to the absence of large communicating branches, and the fixation of the vascular tree by a rigid lining.

Brailsford has pointed out that living bone adjacent to necrotic bone undergoes a rarefaction as seen by roentgenogram. This is regarded as an area of

hyperemia, as the diminution of density in such bones reaches its peak during the healing stage or most active phase of revascularization of the necrotic area. Referring to coxa plana, he describes the process as an osteochondritis, preferring this more inclusive term to avascular necrosis. In the healing of a fracture an area of adjacent hyperemia is also encountered (Urist). Transfer of mineral salt may also occur at this period.

The first change noted in avascular necrosis is death and disappearance of the osteocytes in their lacunae. The marrow spaces fill with debris and later with a dense type of fibrous tissue. The trabeculae remain intact but having lost their elasticity are prone to collapse and impact upon each other as a result of stress.

The appearance of increased density of the necrotic area is said to be relative, the living adjacent bone being hyperemic and perhaps undercalcified as a result of atrophy. However, there are other possible explanations for an absolute increase in density of the necrotic part. Damaged tissue often acquires calcium. Such a biologic phenomenon is often seen following degenerations of tendons in the shoulder and is occasionally seen in scar tissue. The impaction of trabecular fragments may also give the appearance of increased density. Changes in density may result from calcification of the line of demarcation and the presence of new bone bordering the dead fragments.

The first evidence of repair is the presence of a zone of vascular fibrous tissue originating from the adjacent live bone marrow and infiltrating the marrow spaces of the dead bone. This tissue gradually invades and breaks down the dead marrow. The exact mechanism of this process is unknown. From this same vascular fibrous tissue an osteogenetic zone appears, and necrotic bone is invaded and replaced as in a transplant, by a process which Phemister termed "creeping substitution" Invasion, destruction, and replacement advance together in a narrow zone Occasionally the invasion may advance at a more rapid rate and the zone of the activity is expanded.

The above process, however, does not always go on to complete elimination of the necrotic area (Kahlstrom et al) Large areas may only be partially removed. What terminates the reparative effort is not known The occurrence of a fracture through the weakened zone of transformation with disorganization of the invasive tissue is a deterrent to further repair, but is not an absolute block.

When the necrotic area borders a joint, damage to the articular cartilage may result. This may follow collapse of the supporting subchondral bone secondary to stress, or result from inadequate cartilage nutrition. During the growth period adequate nutrition to the cartilage may be derived from the synovial fluid, but in adulthood cartilage depends for its nutrition principally upon subchondral vessels and the loss of this circulation for an extended period allows degenerative changes to occur Phemister places the interval at one year although he states that good function may result in aseptic necrosis of the femur up to three years.

During the growth period the articular cartilage is damaged less frequently than in adulthood following necrosis. The reparative process is more rapid

and usually fully completed while the hyaline cartilage receives adequate nutrition from the synovial fluid during this age period. Brailsford believes that in coxa plana, the hyperemia of the repair process results in an increased plasticity of the replaced area and adjacent bone which persists for three or more years.

The life history of a bone transplant is histologically similar to regeneration of necrotic bone. The question of whether transplanted bone cells survive or die is of paramount interest. Does a bone graft like an autogenous skin graft, live to be nourished on host tissues or does it play a passive role and simply encourage new bone formation?

Most of the experiments in recent years indicate that the greater portion of the graft dies and is replaced by host bone. Endosteal cells lining the graft edges, however, are thought to remain alive and proliferate if they are rapidly reached by growing vascular tissue from the host. It is evident that when the number of surface osteocytes is great, much of the graft will remain alive.

The trabeculations of cancellous bone offer a much greater surface area than cortical bone, and osteogenesis has been shown to occur more rapidly in such transplants than in cortical bone. In cortical bone only those cells on the endosteal surface are likely to remain alive. The major part of the graft must be invaded, removed, and replaced Flaked and chipped segments of cancellous bone should be superior to large cancellous fragments by presenting a greater number of surfaces. However, there is a limit to this process. Macewen noted that bone chips survived better than bone dust (Bell).

No significant difference in osteogenesis has been noted between grafts with or without attached periosteum. Cells exposed to vascular tissue, whether periosteal or osteal, showed a tendency to proliferate.

Recent work (Abbott et al.) shows that the osteocytes in the transplant were able to remain alive for a period of about 10 days after transplantation without the vascular support of the host. If such granulation tissue reaches the cell before this period, a considerable number of such cells live and produce new bone In cancellous tissue the number of cells which proliferate is marked. Even when cell death occurred, the ensuing "creeping substitution" seemed to be more rapid in the loosely textured cancellous bone than cortical bone. The ingrowing vascular tissue is blocked on cortical surfaces, with the haversian systems offering the only inlet.

The host bed is of importance Not only must the graft be in intimate contact with the host bone, but the recipient area must be a source of rapidly growing vascular tissue

It should be emphasized that our present concept of bone grafts is based almost wholly on a histologic approach. A graft is deemed dead if lacunae lack cells, and alive when osteocytes are seen. There is some evidence of the existence of inductors in bone which stimulate osteogenesis, and such a process may be active in the graft Grafts do not take up dyes and they do not immediately show a loss of density when such a process occurs in the host. If the major portion of a graft is an inert foreign body of formed mineral salt, its successful replacement may be a result of its low capacity for stimulating host reaction and the charging of neighboring tissues with bone mineral.

BONE INFECTION

INFLAMMATION OF BONE

The reaction of bone to an inflammatory process is well illustrated by acute hematogenous osteomyelitis on the one hand and by the chronic granulomatous inflammation of bone tuberculosis on the other. While there are several points in common, the present methods of treatment draw a distinct line between the two conditions, and mainly for this reason they are presented under separate headings.

Acute Hematogenous Osteomyelitis. Acute hematogenous osteomyelitis is seen most often in children. The infection is borne through the blood stream from infected teeth, tonsils, ears, abscesses, or other foci. Boyd states that the metaphyseal areas of the femur and the tibia are the regions most commonly affected, and the reason for this is believed to be that the areas near the epiphyses are repeatedly subjected to trauma. However, both Leveuf and Birkett describe cases of osteomyelitis in children which involve the diaphysis rather than the metaphysis

The blood-borne bacteria lodge in the walls of the metaphyseal vessels. The channels widen at this point and the circulation may be sluggish. If the trabeculae have been injured previously there is already some edema, and under these circumstances the bacteria will flourish. The focus enlarges from within, and the circulation to the region is further impaired. Arteriography of bone lesions has shown that in osteomyelitis there is obliteration of the vascular channels within the affected bone area, but an abundance of vessels is present within the neighboring soft tissues (Dos Santos).

The course of the disease will depend upon the type of the infecting organism, the extent of the local injury, the resistance of the individual, the type of treatment, and when it is begun. When the circumstances are most favorable, the infection may be overcome rapidly enough to leave no definite trace (Nachlas and Markheim). Under less favorable circumstances an abscess may be produced with localized bone necrosis. If, as in the more severe infections, the pus spreads either within the medullary cavity or subperiosteally, the entire bone may be involved If a section of bone is completely surrounded by the inflammatory process its blood supply is interrupted and it dies. This dead bone is known as a sequestrum Destruction and repair proceed at the same time in different areas In the process of healing, if the sequestrum is not extruded through a sinus, it may actually be revascularized and be incorporated into new bone formation. The newly formed bone is dense. Sclerosis of bone in osteomyelitis is common.

The organism most frequently found in osteomyelitis cases of this type is the hemolytic *Staphylococcus aureus* (Altemeier and Wadsworth). Drugs such as penicillin have played a large part in reducing the morbidity and mortality of the disease. Statistics of authors vary, but reduction of mortality rates from a high of 33 per cent to less than 2 per cent has been reported (Altemeier and Wadsworth; Dennison) With the aid of chemotherapeutic agents, the body is better able to localize the infection and to limit its spread. If penicillin is

given within the first few days after onset, there may be complete arrest of the process and eventual restitution of the bone to normal.

Roentgenograms can follow graphically the course of the disease. While soft tissue reaction is the first sign noted, periosteal reaction is usually not evident until the second week At that time there is a decreased density within the metaphysis With the formation of pus, holes may appear in the cortex, and as the pressure within the bone builds up, the periosteum may be lifted away from the diaphysis A sequestrum may be evident as a dense bony spicule or segment With healing, sclerotic bone is formed. The degree of sclerosis is thought to be less in cases adequately treated with penicillin (Altemeier and Wadsworth).

Tuberculosis of Bone Tuberculosis of bone is considered to be a local manifestation of a general disease The original site of the infection is believed to be in the bronchial or mesenteric lymph nodes From the primary focus the bone is invaded, usually through the blood stream, but occasionally it may be invaded directly from neighboring tissues The bone infection is frequently associated with tuberculosis of the neighboring joint or joints. In the long bones, it is the metaphyseal region which is most often involved (Mercer).

Elsewhere in the body tuberculosis can produce destruction, caseation, or fibrosis The same is true of the disease in bone. The destructive phase is, however, usually more obvious than the phase of bone formation A tubercle is formed with a central group of endothelial cells surrounded by a zone of lymphocytes Fresh tubercles multiply in the surrounding area. Dense fibrous tissue develops as an attempt is made to wall off the lesion, and the lesion may itself be invaded by connective tissue with resultant healing

The bony trabeculae may show evidence of osteoporosis in some areas and of osteosclerosis in others. The osteoporosis is thought to be due in part to the *pressure and erosive influence of the granulation tissue produced in the process* (Boyd, 1947)

Boyd recognizes two main types of bone tuberculosis: first, the localized type, and secondly, the spreading type In the former condition the disease is held in check even though small sequestra may be found within the area In the second type the resistance is insufficient to limit the spread of the disease, and the process will frequently spread to involve the epiphysis or the neighboring joint in a caseous purulent inflammation

Since the advent of streptomycin as a therapeutic agent in the treatment of tuberculosis of bones and joints, encouraging reports have appeared (Pulaski et al, Ralston). In a council report of a series of 94 cases, in which 70 per cent of the bone lesions were becoming worse prior to streptomycin therapy, a definite reversal of this trend followed administration of the drug, for at the end of the post-treatment observation 70 per cent showed improvement roentgenographically The belief is that there is slow but appreciable improvement in the majority of tuberculous lesions of bone and joint treated by the method described Whether the improvement is long-lasting awaits further observation.

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The Medullary Fixation of Fractures

Medullary Fixation of Fractures*

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HISTORICAL

The principle of axial pinning or medullary fixation is not new in the treatment of fractures. However, it is only within the last decade and following the work of Kuntscher that it has attained acceptance and wide employment. Axial pinning was apparently first used by Lambotte about 1907 in the treatment of fractures of the clavicle. Here he first employed a screw and later a grooved nail. He also used screws about 5 inches in length for axial fixation of subtrochanteric fractures of the femur.

In 1913, Konig introduced the use of intramedullar ivory pegs in fractures of long bones. During the next five years ivory and bone pegs were quite commonly, though often unsuccessfully, employed. Failure was apparently due to "sending a boy to do a man's job." Hey Groves reports that the grafts, if snug, frequently broke, while if loose they provided poor fixation. Having once broken, they acted only as plugs in the medullary canal preventing endosteal callus formation.

In 1918, Hey Groves treated 3 cases of fracture in the proximal third of the femur by a method closely resembling that of Kuntscher. In all he used a steel bar which filled the diameter of the canal, in the first case a perforated steel tube 9 inches in length, in the second a rod with cross-shaped section, and in the third a round rod. These he passed retrograde up the proximal fragment and through the trochanter, then down a distance of 3 inches into the distal fragment. All 3 cases were septic compound fractures and his difficulties were those of infection rather than lack of fixation.

About 1924 Lambotte extended his nailing method to include transverse fractures of the proximal end of the humerus, lower end of the radius and ulna, also metacarpals and phalanges In Belgium also, according to Soeur, Joly used Kirschner wires for axial fixation of fractures in the clavicle, metacarpals, phalanges, toes, carpal scaphoid, malleoli, and humeral head about 1935, while Danis recommended the same agent for bones of the forearm and fibular malleolus.

In this country in 1937, L. V. and H. L. Rush implanted a Steinmann pin in the medullary canal of an ulna for fracture in the proximal third, and in 1939 in the femur for subtrochanteric fracture These were left protruding through the skin and were removed after eight and nine weeks, respectively.

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In England, Lambrinudi reported on the use of Kirschner wires for 2 cases with fracture of both bones of the forearm and one osteotomy of the femur. The wires were removed at four, five, and six weeks, but the extremities maintained in casts several months.

KÜNTSCHER'S METHOD

Kuntscher in 1940, apparently unaware of Hey Groves' work, presented the method which has since borne his name. He successfully attempted a fixation for shaft fractures analogous to nailing in the femoral neck. The fracture was reduced by manipulation; the end of the nail was covered by soft parts so that early removal was not necessary, but readily possible after union had occurred. The nail was of sufficient size to span the canal, preventing lateral displacement; also, long enough and strong enough to prevent rotation and angulation even though external fixation was not used.

Kuntscher's method spread rapidly over Europe because of many war casualties for which it seemed ideally suited Also because of the war and its interruption of the flow of European periodicals to this country, our first acquaintance with the method was through prisoners returning with nails in situ. It was not until 1945 that surgeons here commenced inserting such nails

Theoretical Disadvantages

From the outset the method has been called unphysiologic since such a large piece of metal is employed The risk of infection which accompanies any open operation involving bony structures is still of major importance, even with the newer drugs While it is true that serious infection rarely develops in simple fractures treated in a modern surgical clinic where strict asepsis is maintained, there is still the occasional infection, be it air-borne or through faulty sterile technic. It is not uncommon to obtain a positive culture from beneath a plate on its removal even though there has been no clinical evidence of infection Then too, we have the ever-present problem of compound fractures in which the degree of contamination is always an unknown quantity. It is the consensus that closed nailing carries less risk of infection than open reduction with any other type of fixation. Whether the same can be said of open nailing is more subject to debate. However, the length of incision, amount of bone exposed by the incision, and the duration of the operation are all generally less with medullary nailing The course of the infection once it is established in a case with nailing may be more severe. Soeur bars the use of a nail in all compound fractures. Heim reports good results in treating gunshot fractures of the femur by closed nailing after a period of two to three weeks in skeletal traction and giving sulfonamides, initial debridement having been employed Bohler advocates Heim's procedure for gunshot fractures where the soft tissue wounds are small He also treats fresh compound fractures by debridement and open nailing, but closes only the skin layer The only compound fracture among our 35 cases with fracture of the femur had only a small puncture wound. He was treated by wire traction for two weeks while receiving penicillin. Since no evidence

of infection was shown then, a closed nailing was performed which was followed by uncomplicated union.

Fat embolism has been feared from the start and much discussed, since a major portion of the displaced marrow is fat. Experience, however, has proved that the incidence is no higher than in fractures treated by other methods. In our series, one patient with bilateral fracture of the femur developed hemiplegia 24 hours after injury while in skeletal traction before any nailing was attempted. Burr holes failed to reveal any intracranial hemorrhage. He gradually recovered and the final clinical impression was that he had sustained a fat embolism Subsequent nailing of both femurs produced no further signs of this condition. Subclinical fat embolism is apparently a frequent occurrence, however, as evidenced by the appearance of fat droplets in the sputum. Experimental work of Maatz demonstrated slight fat embolisms in animals following nailing. In his opinion, fat embolism following nailing becomes of clinical importance only when the patient is in severe shock. The superimposed embolism may then contribute to a fatal outcome. This is easily avoided by delaying the operation until the general condition has improved. Embolism of blood thrombus has occurred to my knowledge in one case which was nailed three weeks after injury. There is nothing in the operation of nailing which would induce this complication more than any other manipulative procedure, but it should be considered when late operations are contemplated.

The destruction of red marrow is not of significance, for considerably more is lost in amputations. Slany found an increase of reticulocytes persisting while the nail was in place, and in some cases an anemia Whether this was the result of blood loss or toxic effect of the metal used would require further study to determine. Schuettemeyer was unable to find such changes in 600 cases. It has not been of clinical significance in any of our cases

The criticism that the nail destroys endosteal circulation and interferes with endosteal callus formation is frequently made. As Kuntscher originally noted, the nail does not completely fill the canal as did the bone pegs, but impinges only at a few narrow places. That pressure of cortical surfaces stimulates callus formation and union while distraction does the reverse, has been clearly shown experimentally by Eggers, Shindler, and Pomerat. In Kuntscher's method the union between the bone ends is apparently enhanced by moderate pressure and periosteal callus unimpaired, also, the fracture is controlled with respect to displacement, angulation, and rotation for an indefinite period by the nail Such being the case, the method appears to be ideal whether endosteal callus develops or not

The question of callus formation has been much debated. Kuntscher, Soeur, and others reporting early cases, described the callus as exuberant and rapid in forming, and listed this as an advantage of the method. Bohler has found an inhibitory effect of the nail He states that earlier cases with exuberant callus or "periosteal appositions" were ones in which a short nail had been used, permitting some angular motion. Recent experimental work of Fitts et al indicates more extensive callus when a nail is employed Our cases thus far indicate neither stimulation nor inhibition of callus formation. It is no less than in other cases in which solid fixation has been obtained.

Advantages of the Method

The primary advantage is that of early mobilization. Since no external fixation is necessary, motion of the joints may be started as soon as soft tissue healing permits — usually within a few days. Therefore, joint stiffness and muscle atrophy do not occur as in treatment by external fixation The patient can leave the hospital at two to three weeks, no longer requiring nursing care, and without the discomfort of casts or improperly supervised makeshift traction devices at home With elderly patients, the fact that they can be out of bed early has the *same importance as in fractures of the femoral neck and may be a life-saving* measure A 74-year-old woman, whose femur was fractured in the lower part of the mid-third returned home in a wheel chair two weeks after we inserted a nail. Early ambulation allows the patient earlier return to work, and may mean the difference between retaining his former job and the need to seek other employment Bohler presents a case in which there was no apparent disability at eight weeks following fracture of the femur, while at 10 weeks the patient underwent a strenuous course of military training without symptoms. A patient of ours returned to work as a machine shop apprentice at seven weeks and continued without discomfort until recalled for removal of the nail at six months. Many similar examples could be cited.

Other advantages are the simplicity of the procedure and the short operative time It also has proved an excellent internal fixation for osteotomy in cases of malunion and for femur shortening

FRACTURE SITES SUITABLE FOR NAILING

The main field for medullary nailing is in shaft fractures of the femur, since other methods of treatment require prolonged recumbency and the duration of disability is great. While the method can be used with good results in the tibia and humerus, the results are equally good with walking and hanging casts respectively, and at the present time we do not recommend it for fractures of these bones. An exception should be made in tibial fractures of the paraplegics, who do not tolerate casts well because of pressure sores, also, in some nonunions of the humerus where the nail, supplemented by barrel stave grafts, is effective. Fractures of both bones of the forearm have always been a problem owing to the difficulty in maintaining alignment. Angulation and displacement are well controlled by axial pinning and there appears to be definite advantage to its use in the forearm Contrary to Bohler, we have found it useful also in fractures of the metatarsals where displacement is often difficult to control by other methods and may lead to considerable disability. It is also of value in some transverse fractures of the metacarpals and widely displaced fractures of the clavicle

The fracture must not be too close to either end of the bone or the nail will not adequately control the smaller fragment The most favorable portion, of course, is the middle third where the canal is the narrowest, and transverse fractures are generally more easily controlled than spiral or oblique. For the femur, Bohler has set the distance at not less than 7 cm from the tip of the trochanter or knee joint. Romney regards these limits as too liberal and places them at 8 cm. for the proximal and 10 cm. for the distal end We consider 12 cm.

the minimum safe distance from the knee joint for a single nail inserted from above. Fractures in the supracondylar region are probably better treated by the method of Rush, inserting a pin through each condyle. For the tibia, the middle third; and for the other bones, the middle half is generally satisfactory.

Types of Nails

The nails originally used by Küntscher were V shaped in cross section. These are still preferred by Westerborn, Brünner, Romney, and doubtless many others. This form was then modified to the clover leaf for the femur to provide greater strength and a narrower entrance to the groove so that the nail would follow the guide pin better. The V or U shape was retained for the smaller bones. An advantage of this form is that two nails can be inserted, one inside the other, and given a slightly different amount of bend so that the points will diverge in the wider canal at the end of the bone. This procedure was perfected by Maatz. Romney utilizes the same principle when a nail becomes bent, by straightening the nail *in situ* and inserting an additional nail.

In his original work, Kuntscher speaks of the flanged nail touching the endosteum at three extremely small places because of the sharp edges. This advantage, and such Kuntscher apparently believed it to be, has been lost to some extent with the clover-leaf cross section since its surfaces are rounder. The diamond-shaped nail, however, not only retains the sharp edges, but impinges at only two points. This nail was designed by Hansen, first used by us in 1945, and presented in 1946 It has since been widely used in this country.

Apparently Hey Groves was the first to investigate the relative advantages of different shapes of nails for the femur He preferred the solid round bar since there were no pockets or crevices to harbor infection. This criticism is applicable to the clover-leaf pattern, in which it would be difficult for the blood supply to gain sufficient access to the deep groove to eradicate infection. It is a secondary consideration that the nail acts as a tube to drain off the pus.

We have recently investigated the relative strength of variously shaped nails in controlling angulation and rotation. Of the forms in clinical use, the clover-leaf showed greater resistance to angulation with the diamond-shape a close second, while the diamond was superior in controlling rotation.

Apparatus

The necessary apparatus depends on the type of nail used and whether a closed or open nailing is performed. The most important item for any medullary nailing procedure is a good extractor, since it frequently is necessary to extract the nail partially or completely during the original nailing, as well as to remove it after the fracture has united. The original extractors had a hook which fitted into an eye in the end of the nail. One of the most satisfactory, designed by Kuntscher, was a C-shaped piece of metal with a hook on one end and a handle and place to hammer against on the other (Fig. 1). The axis of the hook and direction of the hammer blows are thereby in a straight line. Küntscher also devised a windlass type of extractor which was less satisfactory because its counter pressure was exerted against the greater trochanter, the cortex of which is very thin, and it also required greater exposure. The same difficulty was

encountered with a screw type of extractor resembling the Smith-Petersen nail extractor and formerly made by Richards in this country. The second most important type was designed by Stor and consisted of a long bar carrying a heavy sleeve. Blows were struck with the sleeve against a handle at the opposite end from the hook In our experience, the angular acceleration of a hammer blow is more effective than linear acceleration of the sleeve, also the weight of the hammer can more readily be varied. The chief difficulty with all extractors

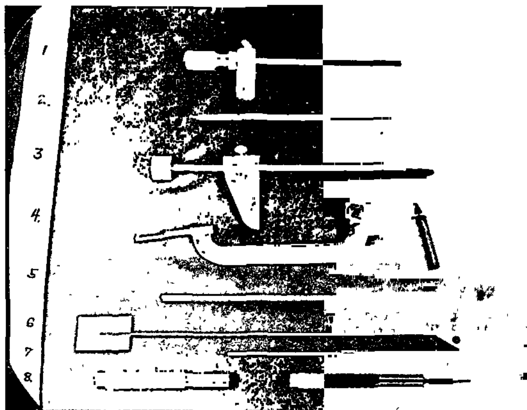


FIG 1 —Special instruments for medullary nailing (1) Driver-extractor for diamond-shaped nail, (2) diamond-shaped nail, (3) modification of Stor extractor; (4) Kuntscher extractor, (5) clover-leaf nail, (6) guide pin for clover-leaf nail, (7) reamer for clover-leaf nail, (8) drivers for clover-leaf nail

has been in making a hook which would neither break nor straighten Westerborn has an extractor with a jaw bearing a pin hinged to the main shaft This closes on the end of the nail like a forceps and is held shut by a slip ring. This should retain a very positive hold on the nail With the diamond-shaped nail, instead of an eye we have used a threaded stud on which the extractor is screwed into place. The same instrument can be used for both driver and extractor, hammering against the longitudinal handle for the insertion, or against the transverse handle for extraction. This is the only special instrument needed for this type of nail other than the usual bone instruments We have been unable to strip the threads on the stud by hammering on the extractor with the nail held in a vise, provided the extractor was screwed on tightly. The illustration shows other instruments used in inserting the clover-leaf nail which will be discussed under Technic of Nailing.

For open nailing, the ordinary operating table is satisfactory. For closed nailing of the femur, adequate apparatus for applying traction is necessary. In Europe the Böhler traction apparatus has been widely used. Soeur states that the ordinary orthopedic table is not suitable but we have had good results employing a common form of fracture table. Reduction apparatus of the Linsmayer or Wittmoser type is almost mandatory if the technic as outlined by Böhler is followed, i e , if the operation of inserting the nail is not begun until after accurate reduction is obtained The technic we employ is that originally described by Kuntscher – the nail being inserted down to the fracture line after which the fracture is manipulated. We have not felt the need for reduction apparatus. X-ray equipment is necessary for both fluoroscopic or roentgenographic control. Two portable units are convenient, though one will suffice. It merely must be shifted from A-P to lateral position perhaps a number of times. We have used the ordinary hand fluoroscope with success, however, the one designed by Heinz Braun and pictured in Böhler's book appears to have many advantages. The usual fluoroscopist's gloves and apron are of course worn.

Besides the usual equipment, it is well to have certain other items on hand for emergencies. A hack saw is necessary if a nail becomes jammed so it can be neither inserted nor extracted. Vise-grip pliers are useful in extracting a nail that has been inserted retrograde and found to be too tight. A bone hook has been used many times as an emergency extractor, gripping the handle with pliers and hammering against the pliers Extra nails of various sizes should also be available.

TECHNIC OF NAILING

In either method the size of the nail to be used is determined prior to operation The diameter of the narrowest portion of the canal (isthmus) may be estimated from the roentgenograms. According to Fischer, if the tube-film distance is 75 cm. the canal is actually 1 mm. narrower than measured on the film. With a distance of 80 cm. Bohler allows 2 mm. for the femur. If the film cassette is directly beneath the thigh 1 mm is approximately correct; however, we allow 1 5 mm Böhler employs a thinner nail if there is marked bowing so it will bend more readily in the canal. We prefer to bow the nail before it is inserted and use a full sized nail To determine the length, the opposite femur may be measured from the tip of the trochanter to the knee joint line and a certain amount subtracted Soeur subtracts 4 cm However, in our experience this is too much. For most cases we subtract 1 inch (2.5 cm) which, when leaving ½ inch projecting from the trochanter, brings the distal end 1½ inches from the knee joint In low fractures, however, we do not subtract any but watch the distal end with the fluoroscope to avoid entering the knee joint.

Open nailing is technically easier than closed. There is, no doubt, greater risk of infection than in closed nailing but with careful aseptic technic and the postoperative administration of antibiotic drugs the risk should be slight. The patient is placed in lateral decubitus on the sound side with both hips and knees slightly flexed. The involved extremity is draped free with stockinette to allow change of position and manual traction (Fig. 2). The fracture site having been exposed, the nail may be inserted either directly from above or retrograde. The latter is technically easier.

If the technic of Bohler is followed, using the guide wire and clover-leaf nail, the guide is first inserted retrograde up the proximal fragment, out through the trochanter, and through a 2 cm incision in the skin A short nail is then inserted over the guide a distance of 1 cm into the trochanter. The guide is then removed from the fracture site and a new guide inserted from above through the short nail. The new guide is then passed down to the fracture site and the short nail removed. The fracture is next reduced and the guide passed into the distal fragment. Roentgenograms are then taken to determine whether the alignment is good, with no angulation, and whether the guide is properly located. The nail is then

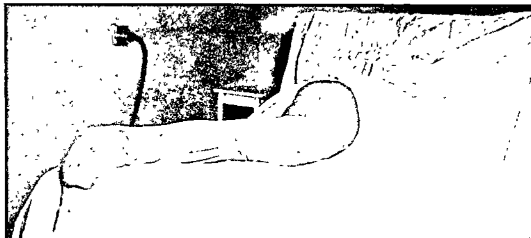


Fig 2 —Position and draping for open nailing of femur.

driven in over the guide using a recessed driver which leaves 2 cm. projecting above the trochanter

A more simplified technic is generally employed for the insertion of the clover-leaf nail The guide is drilled up through the trochanter and the skin incised A reamer is then slipped over the guide and a hole cut through the cortex of the trochanter The nail is driven over the guide in the proximal fragment. The guide is then withdrawn and the nail driven into the distal fragment without a guide and roentgenograms are used only to check the final position.

In inserting the diamond-shaped nail by the open method we introduce the nail into the proximal fragment, pass it up through the trochanter, and incise the skin when the nail can be felt subcutaneous We use a 1 inch transverse incision and cover the skin margin with stockinette. The driver-extractor is then screwed into place and the nail extracted until the tip is at the fracture site. The fracture is then reduced accurately and held with a Lowman clamp, while the nail is driven into the distal fragment The nail may be driven until the driver-extractor strikes the trochanter, in which case the threaded stud will be left protruding from the bone and available for extraction Its removal is easier, however, if it is allowed to protrude an additional one-half inch An advantage of inserting the nail without the use of a guide lies in the fact that the nail accurately follows the axis of the marrow cavity. This is not necessarily the case with a guide pin.

The objection has been raised that driving a nail through the trochanter

without drilling or trephining the cortex may produce an "explosion" fracture of the trochanter. For this reason, we originally screwed a very sharp arrow head point on the threaded stud. Experimental and clinical experience, however, has shown the risk of comminuting the trochanter to be slight with either the arrow head or simply the pointed stud.

Open reduction is required for the following: (1) Revision of callus, (2) osteotomy for malunion; (3) removal of unsuccessful internal fixation; (4) insertion



FIG 3 —Delayed union of the femur, open revision of callus necessary

of supplementary internal fixation, (5) reduction of segmental fracture; (6) femur shortening

Revision of Callus. In fractures treated more than a month following injury, unless alignment has been maintained by some other method, it is necessary to free up the callus to restore alignment The fragments of callus can well be inserted around the fracture line after nailing to serve as supplementary grafts (Fig 3).

Osteotomy for Malunion. In correcting an angulation by osteotomy, a wedge should be removed, making the cut surfaces perpendicular to the axis of the fragments Good apposition of the fragments will then be obtained. This was not completely effected in the case illustrated (Fig. 4).

Removal of Unsuccessful Internal Fixation. The necessity for open reduction to remove a loose or broken plate, screws, or medullary graft, needs no explanation (Fig. 5).

Supplementary Internal Fixation Oblique fractures in the isthmus can be held by means of a medullary nail alone, as also can comminuted fractures in which

less than one-half of the diameter is represented in the intermediate fragment. In long oblique or spiral fractures below the isthmus, and in extensively comminuted fractures in any part of the shaft, supplementary fixation to prevent displacement of the fragments is indicated Böhler has used circumferential wire sutures or wire mattress sutures with good results. We prefer screws in most cases since the fixation is more positive (Fig 6). The screws are placed through a lesser chord than the diameter, preferably remaining within the cortex for



FIG 4.—Osteotomy for malunion of the femur.

their entire length and thereby avoiding the nail The comminutions are generally attached to the main fragment presenting the longer fracture line only, provided the other line is short This converts a comminuted fracture into a transverse one and the telescoping effect of the nail can still operate.

Segmental Fractures. Fractures composed of one or more tubular segments are ideally treated by this method, the fragments being threaded like beads onto the nail. Alignment is often impossible without open reduction and longitudinal fissures are common, requiring supplementary screws (Fig. 7).

Femur Shortening Shortening is indicated in repair of extensive nerve or vascular injury, or more frequently to equalize a shorter opposite extremity. Both cuts should fall within the isthmus to avoid a loose fit of the nail and possible displacement. A long cut surface allows more contact for healing than a transverse osteotomy. The surfaces must, of course, be congruous to provide close apposition. We prefer a serpentine cut which is easily accomplished by drilling a series of small holes with a jig to provide the pattern. Difficulty may be experienced in closing the gap between the bones or in closing the wound if a

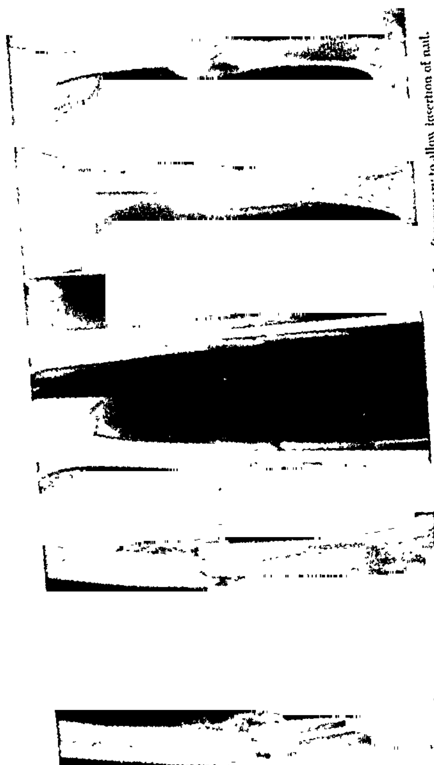


FIG 5.—Delayed union of the femur with fracture of beef bone graft. Removal of graft necessary to allow insertion of nail.



FIG 6 —Comminuted fracture of the femur; supplementary screw fixation was necessary.

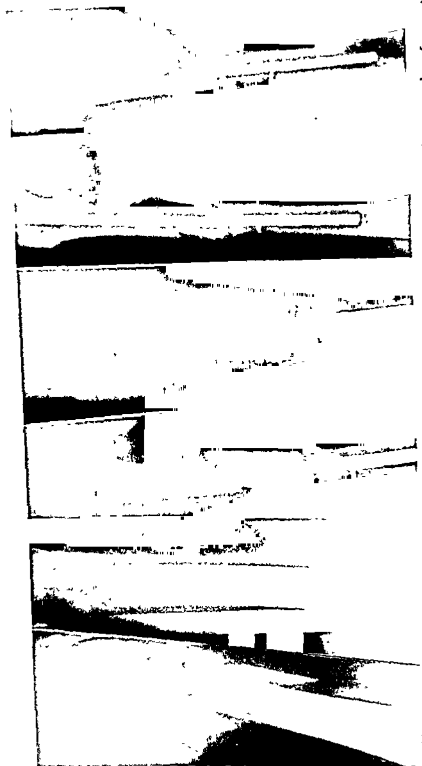


Fig. 7.—Segmental fracture of the femur. Supplementary fixation was necessary for longitudinal fissure in the intermediate fragment, also for other comminutions.

large section of bone is removed. It is then necessary to strip the periosteum a short distance on both fragments.

Closed Nailing

Küntscher has advocated nailing by the closed method whenever the situation permits, chiefly to avoid risk of infection. Surgeons in this country tend to regard this danger more lightly. There are other factors to consider such as the surgeon's experience and aptitude in manipulation, the equipment available, and the physical type of the patient. Fractures are hard to manipulate in the short-boned, heavy-muscled type of patient, particularly if overriding has been present. Certainly there is less risk of complication in a well executed open reduction than in the "hours long wrestling matches" which have been reported in the European literature or even in the one hour time limit advised by Küntscher. Besides the mechanical trauma there is the risk of overexposure to x-rays for both the patient and surgeon. Our longest closed manipulation, which was on a very muscular individual, occupied 20 minutes with a total radiation time of two minutes at 1 m.a. The other patients have required much less time.

The technic as outlined by Böhler involves placing the patient in lateral decubitus and applying traction by means of the Böhler or similar apparatus. This is supplemented by reduction apparatus to displace the fragments transversely in any and opposite directions. The Linsmayer type employs wide cloth straps which form slings around the thigh, one above and below the fracture site, and tightened by rolling on a rod equipped with a ratchet. The Wittmoser apparatus consists of two wooden rings which encircle the thigh above and below the fracture. These are moved by worm gears medially or laterally, anteriorly or posteriorly, to give any desired positions. Two portable x-ray units are used to give biplanar control. Fluoroscopy screens are fastened to the reducing apparatus and the room is darkened. When accurate reduction has been obtained, this is corroborated by roentgenograms and if satisfactory, the nailing is commenced. If considerable force is exerted by the worm gears and the position held for a long period of time, considerable muscular contusion appears possible. Perhaps a lever device such as described by Herzog, in which the pressure is sustained manually, would be safer. It is interesting to note that Küntscher still uses only the longitudinal traction apparatus.

The insertion of the nail is then accomplished through a small skin incision just proximal to the trochanter, making a hole with an awl in the medial side of the trochanter and passing a guide pin down into the distal fragment. Position of the guide is then determined by roentgenograms and if satisfactory, the nail inserted over the guide.

The closed method as we have used it is modified considerably. The patient is placed in lateral decubitus on an ordinary fracture table. The involved thigh is uppermost with the hip flexed to an angle of 110°, the other hip somewhat less. The usual perineal post is replaced by one 12 inches long which provides countertraction against the pelvis just beneath the anterosuperior spines (Fig. 8). The Kirschner wire traction previously inserted is advantageous, allowing flexion of the knee and thereby relaxing the hamstrings. A vertical draping is used to separate a sterile operative field from an unsterile manipulative field and there

is no excuse for contamination (Fig. 9.) The vertical drape contains a sterile glass window to allow the assistant inserting the nail to view the position of the leg. The margins of the 1½ inch incision are protected with wound towels. We have used a narrow osteotome to make a small hole in the medial side of the tip of the trochanter, inserting it and giving it a one-quarter turn; an awl might be better. The diamond-shaped nail is then inserted and driven down to the fracture site. The surgeon, protected by lead gloves and apron, reduces the fracture with the aid of the assistant who has excellent control over the proximal

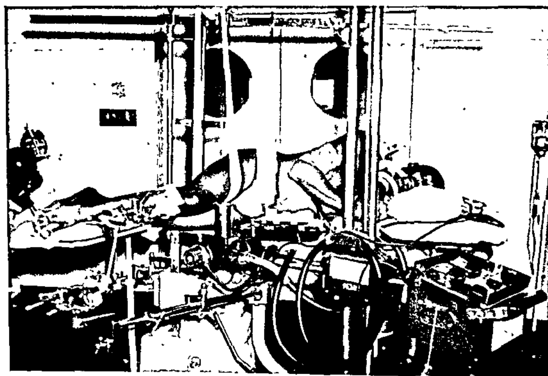


Fig 8 – Position for closed nailing of femur. Kirschner wire traction permits flexion of knee, high perineal post provides countertraction

fragment by using the nail as a lever arm. When the fracture is in position as shown by quick looks with the head fluoroscope, a few taps on the nail by the assistant serve to stabilize the fracture. It is then checked in both planes to ascertain that the nail is in the canal. The fluoroscope is then shifted down to the knee and the insertion of the nail is observed, also the proximity to the knee joint. In certain fractures, reduction has been found easiest by angulating the fracture and hooking the end of the nail in the canal of the distal fragment, as described by Kuntscher. By using a small cone on the x-ray unit, the current may be reduced to 1 m a. and the spot falls within the screen.

PREOPERATIVE AND POSTOPERATIVE TREATMENT

Many advocate immediate nailing of the femur, but we prefer to place all such patients in Kirschner wire traction for a period of observation – usually about seven days This allows the subsidence of the swelling which often

develops before the patient is in sufficiently good general condition for operation If fat embolism should occur as the result of fracture, it is usually in the first 24 hours, and if the fracture had been immediately nailed we would wonder if the nail were responsible. Such a period of observation allows time to rule out infections in other parts of the body, complete the laboratory studies, obtain adequate roentgenograms, and review the nailing apparatus, which is sometimes



Fig 9 —Draping for closed nailing of femur Vertical drape separates sterile operative field from unsterile manipulative field

difficult to accomplish before swelling has developed Habler advocates a period of five to six days in strong traction to correct overriding, thereby facilitating the reduction.

Following operation, the possible need for supplementary external fixation must be considered Most adequately nailed fractures in the isthmus do not require cast or traction, however, rotation will occasionally occur. There is definite risk of rotation if the fracture is at the junction of the middle and lower thirds. To prevent this, a Braun frame is commonly employed Rush uses a plaster splint for about ten days We prefer a balanced suspension using a Thomas splint with Pierson attachment because the knee and hip can be exercised as soon as pain permits Patients vary considerably in this respect, but most have a good range of motion without pain at one week To put a patient in a cast nullifies the chief advantage of nailing — namely, early mobilization.

If a cast seems necessary owing to the type of fracture – such as a long oblique or spiral fracture below the isthmus – supplementary internal fixation should be employed. Traction postoperatively is also inadvisable because it may cause distraction and delayed union. Böhler clearly illustrates the effects of distraction on callus formation and Rush reports his only delayed union in cases where traction was used postoperatively. Most patients may bear partial weight with crutches at three weeks and discard the crutches at six weeks. Earlier ambulation is of no particular benefit and may cause decreased stability.

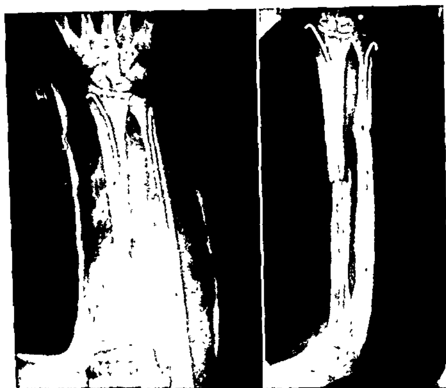


FIG 10 – Fracture of both bones of the forearm Excellent initial reduction was not well maintained by wires Subsequent narrowing of interosseous space

Opinions vary widely concerning the proper time for removal of the nail. Kuntscher and Maatz advocate removal at three months, Socur three to five months, and Bohler six to seven months. We see no cause for hurry and prefer to remove the nails after about one year. Some nails are removed easily and some with considerable difficulty to which many factors doubtless contribute. A patient of ours had bilateral fractures at the same level, nailed at about the same time with identical nails. After nine months the removal of one was very easy while the other was extremely difficult.

OTHER BONES

Fractures involving both bones of the forearm have resulted in considerable disability owing to angulation, displacement, and rotational deformity which cause limitation of pronation and supination. In fractures of the proximal third

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to bury the end of the nail in the bone. In the case illustrated (Fig. 11), the nail protruded rather far but caused no discomfort. In the ulna, a wire may be inserted through either the styloid or olecranon, however, a threaded pin or Kuntscher nail is best inserted through the olecranon. Fractures involving only



FIG 12 —Fracture of one bone of forearm Position adequately maintained by wire and union solid

one bone of the forearm unite more readily and a wire is adequate (Fig 12). In fractures of the metatarsals and metacarpals Kirschner wires have proved satisfactory (Figs. 13 and 14) By inserting the wire through the margin of the base rather than through the head, full function of the joints is permitted with the wires in place. It is safer to cut the wire and place the end subcutaneously than to allow it to remain protruding through the skin.

Fractures of the clavicle with wide displacement are sometimes difficult to approximate by other methods (Fig. 15), and here again Kirschner wires have given good results. Closed reduction is inadvisable owing to risk of damaging the nearby vessels or nerves. Rather than inserting the wire directly from either the proximal or distal ends, we have found it simpler to pass it retrograde through

of the radius and distal third of the ulna, the dilemma is complete because a position of supination is necessary for the radius and pronation for the ulna. The tendency toward nonunion in the ulna is not decreased by plating even though the fracture is well stabilized. At first we treated these fractures by means of axial Kirschner wires, believing the healing process would be less



FIG 11 —Malunited fracture of radius and nonunion of ulna Treated by medullary nailing

affected. Results were improved anatomically, however, deficiencies in fixation still existed. Rotation of the fragments was not controlled and supination deformity of the proximal radial fragment sometimes occurred even though casts were employed. There is also a tendency for the radius to straighten gradually, decreasing the interosseous space even though proper bowing is present initially following the operation (Fig. 10) Wires can be inserted near the tip of the radial styloid, the wire acquires a reversed curve in reflecting off from the opposite cortex that helps to maintain the bow of the radius. This is not the case with the use of a nail, and it must be inserted on the dorsal aspect of the radius more in the region of Lister's tubercle. Dehne has seen two cases of delayed rupture of the extensor pollicus longus tendon following nailing. For this reason, we have employed a cast including the thumb It might be well

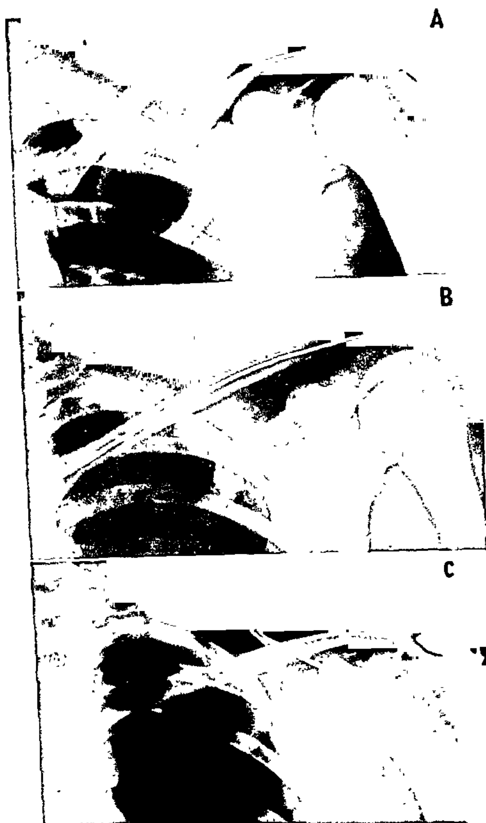


FIG. 15.—Fracture of the clavicle treated by open reduction and retrograde insertion of wire through the distal fragment.



Fig 13 —Fracture of second and third metatarsal necks Wires are inserted through the base of the metatarsals.

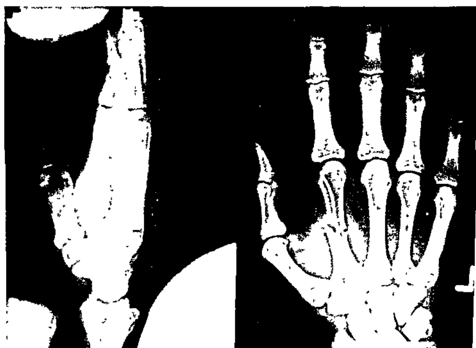


Fig 14.—Fracture of second metacarpal Closed reduction and insertion of wire through metacarpal base



FIG. 15—Fracture of the clavicle treated by open reduction and retrograde insertion of wire through the distal fragment.

the distal fragment and out the posterior of the shoulder, then back into the proximal fragment, clipping the wire to render it subcutaneous.

COMPLICATIONS

These may be divided into those incident to the operation and complications of healing. The operation should not be undertaken until good general condition has been demonstrated The difficulties of the procedure apparently result from



FIG 16—Angulation following insertion of medullary nail The nail was too short and the undisplaced comminution of the distal fragment was overlooked in the original roentgenogram

lack of familiarity with the technic or inadequate equipment. If the nail is too large it may cause distraction, may split the bone or become jammed so it cannot be either driven in or extracted. The last is more likely with a nail permitting cross sectional compression than with a solid nail. If the nail is too small it allows lateral displacement, controls rotation and slight angular motion less adequately, and being weaker is more likely to bend. In our experience an 11 mm. nail has been suitable for a large majority of femurs and one will rarely require an 8 mm. nail Nails which are too long might be driven into the knee joint, but this should not occur if the position is observed with the fluoroscope Certain complications are peculiar to the use of a guide pin. One too thin may slip out of the groove or become jammed therein, while one too thick may stick in the nail and be carried along If defective, the guide may break. Corrosion of the nail has been a complication in some cases in Europe when it was difficult to obtain nails of high grade steel. We have had no trouble from this source either with the steel used in our original nails or with the usual S M.O. #316.

Complications in healing result from infection or the use of a nail which is

too short or too thin. Infection may appear at the site of insertion only and respond readily to treatment without involving the fracture site. This is reported by Böhler in 5 out of 168 simple fractures of the femur and by Habler in 3 out of 140 nailings. Reich reports involvement of the fracture site in 8 out of 740 nailings of simple fractures or 1.1 per cent. Infection may lie dormant only to flare up when the nail is removed. In one of our patients (Fig. 5), positive culture was obtained at the time a broken medullary graft was removed and nail inserted. He showed no evidence of infection following nailing. However, one year later when the nail was removed, he developed pain and swelling at the fracture site followed by drainage from the site of extraction.

Short nails are responsible for most rotation, angulation, and occasionally comminution of one of the fragments (Fig. 16). Migration of the nail proximally may also occur in such cases. We have seen several migrate about one-half inch in the first few weeks before the fracture has become solid, then remain stationary. Fatigue fractures of the nail have been reported following inadequate stability.

As Bohler has emphasized, the operation is purely elective and can be terminated at any stage if complications develop. If the advantages of the method are to be realized, complications requiring the use of external fixation should not occur.

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Arthrodesis of the Spine

Arthrodesis of the Spine

LENOX D. BAKER, M.D. AND WALTER A. HOYT, JR., M.D.

INTRODUCTION

THE PURPOSE OF this chapter is to describe the various methods for arthrodesing the spine. Indications for the operation will not be discussed in detail except when such a discussion is needed to clarify a specific purpose for the procedure. The general indications for arthrodesis of the spine are as follows: (1) Unhealed tuberculosis of the spine except when contraindicated by the patient's general condition In the past draining tuberculosis sinuses have sometimes been considered as contraindications for operative fusion, however, since the introduction of the antibiotics, particularly streptomycin, this point is debatable and further studies are needed. (2) Scoliosis, when there is a rapidly developing curve, when the deformity is such as to interfere with the normal body processes, or in the presence of severe pain. (3) Congenital abnormalities, such as spondylolisthesis, when such changes are associated with pain unrelieved by conservative therapy. (4) Following removal of ruptured or degenerated intervertebral disk, especially if instability can be demonstrated or when there is narrowing of the intervertebral space with adjacent osteochondrosis of the vertebral bodies. (5) Compression fractures, associated with disabling pain which is partially but unsatisfactorily relieved by rest or braces. (6) Dislocations, especially in the cervical area. In considering indications for arthrodesis of the spine and in considering the type of operation needed, one should remember that the principles of the operation are to fuse the involved vertebrae in an attempt to arrest disease, to prevent or correct deformity, or to relieve pain If the operation cannot be expected to fulfill one or all of these principles, it should not be attempted.

CHOICE OF METHODS

In presenting the various operative procedures no direct effort will be made to show a choice The choice of methods is summarized satisfactorily by Howorth. "It matters not so much how a particular chip is laid or from whence a particular fragment of bone comes, but as to whether fusion is obtained, how quickly and how strong" Controversial points will be presented; decisions will be left to the reader as they apply to individual cases. Every reasonable care has been taken to give credit to the originator of new procedures and to those who have described modifications of old procedures. In those instances where similar procedures have been reported by more than one author, only one report will be included.

In 1911 Hibbs and Albee, working independently, described operative procedures for arthrodesis of the spine. Hibbs developed a method of fusing the spine by multiple small osseous flaps from adjacent spinous processes, laminae, and articular facets. Albee used a curved cortical graft from the tibia reinforced by cancellous bone. The success of these operations in the treatment of tuberculosis of the spine led to their wide acceptance and to their use in the treatment of other problems relating to the back. Failure of the operations led to much controversy as to the merit of the procedures. The arguments served to bring out the strong as well as the weak points of both methods and led to other workers describing many modifications and combinations of the two operations

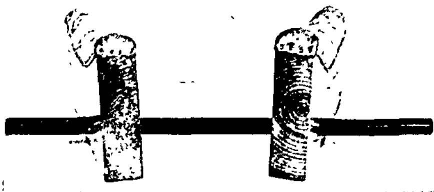


FIG 1 —Henry and Geist shoulder rest.
(Henry, M. O, and Geist, C S: *J Bone & Joint Surg*, *15* 622, 1933)

LEVEL OF FUSION

At operation it is often difficult to identify the exact level to be fused Marking and confirming the level before operation may be done by several methods. In this clinic, a pin-point spot is tattooed with methylene blue just to the side of the spinous process to be fused. A hypodermic needle is inserted through the spot and the exact level is determined by a lateral roentgenogram. The needle is removed and the tattoo mark is used as a guide.

SUPPORTS

So as not to embarrass respiration during operation, a shoulder rest, as described by Henry and Geist, or the horse-collar shaped pad described by Chandler is used to raise the thorax slightly from the operating table (Figs 1 and 2).

Intravenous infusion of saline and glucose is recommended at the beginning of the operation. In this clinic, in addition to the intravenous saline and glucose, blood transfusion is started routinely at the beginning of the operation.

The choice of anesthesia does not differ from that in other major surgical procedures and depends largely on the patient's general state.

INCISION

Albee employed a curved incision starting in the midline two or three vertebrae above the area to be fused. The incision swings to one side of the midline and ends in the midline well below the diseased area. Many operators use a midline incision, especially those who employ a Hibbs type technic where the spinous

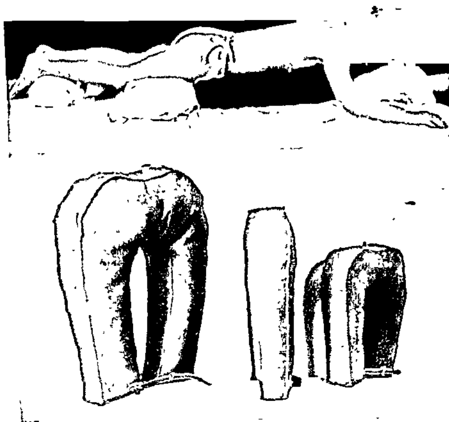


Fig 2.—Horse collar shaped hair mattress pad for shoulder rest and chest protection (Courtesy of Dr Fremont A Chandler)

processes are removed When the spines are left at full length, the curved incision is preferable as it places the skin incision to one side of the prominent spines and the graft.

HIBBS' ARTHRODESIS

Hibbs, in his first 3 operations, made no attempt to fuse the laminae or the articular processes. He described his first operation as follows: "This operation was done through a longitudinal incision directly over the processes, the ligament was split, the periosteum of the processes removed very carefully and retracted with the muscles. The processes were divided at their bases as closely as possible without opening the canal. Then they were placed longitudinally so that there was fresh bone contact, one in the proximal, touching the lower part of the fresh base from which the process was removed, and the distal end

in contact with the upper part of the base from which the next process removed, and so on throughout the diseased area, so as to ankylose the disea one to healthy vertebrae above and below" (Fig. 3). The operation was formed on January 9, 1911. A lateral view roentgenogram made on April 5, 1 and reproduced in Hibbs' original article demonstrated excellent bony fusion the 4 operated spinous processes

In the evolution of spinal fusion Hibbs added fusion of the laminae anc

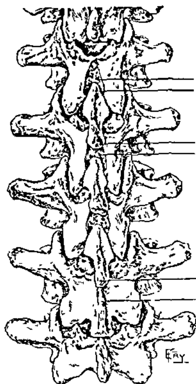


FIG 3 —Illustration of Hibbs' original fusion, which shows his scheme of using the spin processes for solidifying the posterior aspect of the neural arch The processes have been across at their bases as closely as possible without opening the canal They have been placed longitudinal positions so that the upper portion of the cut spine touches the lower part of fresh base from which it was cut and the distal portion of the base from which the next proc was removed In this, his first operation, no attempt was made to utilize the laminae or articular facets in the fusion.

(Hibbs, R A · *New York State J Med*, 93 1014, 1911.)

the articular facets The principle of the Hibbs operation has remained the sa but there have been many useful minor modifications The Hibbs procedure described by Howorth is, in general, as follows: A midline incision is ma through the skin and subcutaneous tissue. After the skin is draped the de fascia and the supraspinous ligament are incised longitudinally. A coagulati cautery may be used to control the deep bleeding The supraspinous ligame is stripped from the spinous processes subperiosteally. The interspinous ligamen are then incised longitudinally. With sharp periosteal elevators the periosteu is stripped from the spinous processes and laminae far enough laterally to expo completely the lateral articulations. Large Hibbs packs inserted tightly as eac

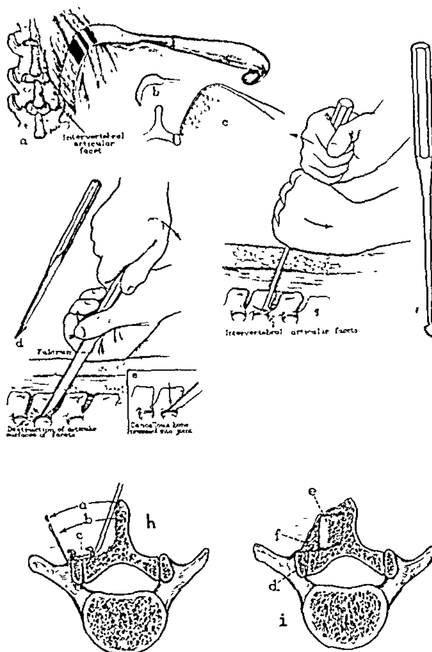


FIG 4 —Meyerding's instruments used in denuding and abrading the articular facets (a, b, c) Exposure of intervertebral articular facets by special retractor (d, e) Small, sharp chisel for destruction of articular surfaces of facets, method of use, and impaction of cancellous bone into the denuded joint. (f, g) Small, sharp hand type of saw and method of use for further destruction of articular facets and the subchondral bone of these articulations. (h, i) Preparation of bony bed and placement of grafts

(Meyerding, H W *Surg*, *Gynec & Obst.*, 94 50, 1947)

lamina is exposed help to control bleeding and aid in stripping the periosteum. The spinous processes are cut across at their bases and removed to be cut into long thin fragments which are eventually laid across the interlaminal spaces. The ligamentum flavum attachments are cut from the superior margin of the

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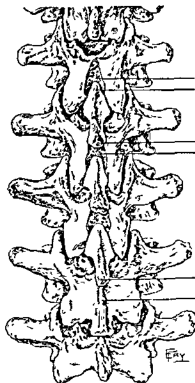


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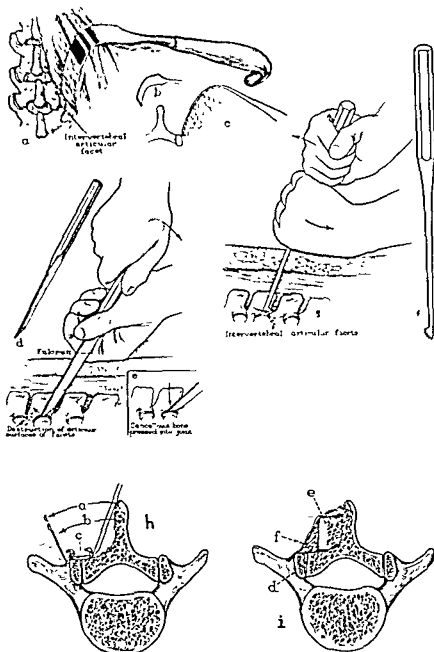


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distal lamina and from the inferior margin of the proximal lamina, which overhangs it. The ligament is largely removed with a sharp curet, leaving only the thin anterior layer of the ligament with the upper and lower edges of the laminae well exposed. Howorth has pointed out that it is important to remove carefully

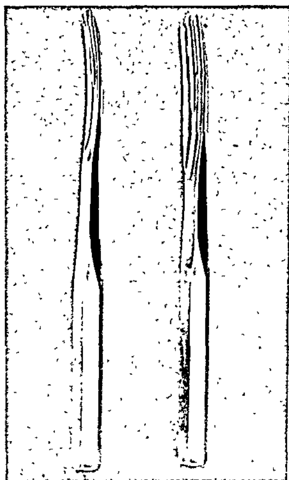


FIG 5—Curved gouges as described by Meyerding used for taking grafts from the sacrum and laminae It is an excellent instrument for denuding articular cartilage from the facets, particularly when the facets face in an oblique plane
(Courtesy of H W Meyerding)

all the ligament from the small fossae adjacent to each lateral articulation. The lateral articulations are then denuded of their articular cartilage with a sufficient amount of the underlying cortical bone to expose good bleeding surfaces. When the articular surfaces lie in the sagittal plane the joints are best excised by a straight, sharp osteotome If the joints are situated obliquely they should be denuded by specially angled osteotomes

Meyerding has described excellent instruments for denuding the articular facets (Figs. 4 and 5). When the articulations are completely denuded, small fragments of bone are cut from the adjacent edges and jammed into the gap between the articular processes. The chips may be supplemented by additional

grafts. When the fragments are completely impacted they should form a compact mass filling the entire excised area. Next, small, slender, but long grafts are cut with a gouge from the laminae and turned across the interlaminous spaces; the grafts interdigitate and are left attached at their bases as much as possible. Then the fragments prepared from the spinous processes are laid longitudinally across the interlaminous spaces. The careful placement of these chips is of greatest importance. If the grafts are placed in a haphazard manner lying in any direction, the chances of pseudarthrosis are greatly increased. If there is not sufficient bone, additional bone from the iliac crest or tibial crest or from a rib may be used, as advocated by Ryerson (see procedures described by Henry, Lewin, Petter).

Postoperative Care

For postoperative care Howorth points out the importance of the general care of the patient and emphasizes the need for postoperative fluids, transfusions, and adequate diet. He recommends immobilization of the spine by bed rest and a brace or plaster jacket until the fusion has become sufficiently strong to support the weight of the trunk and ordinary body movements In turning, the patient should be rolled in such a way as to move the trunk en masse. For simple anomalies or compression fractures, bed rest for six weeks to be followed by a brace for a total of four months is recommended by many (see procedures of King and of Chandler). In the care of the patient with spondylolisthesis, scoliosis, or tuberculosis, bed rest for 12 weeks is thought advisable and the wearing of a support for an additional three to six months.

ALBEE TECHNIC

Albee, in his original description of the operation now known by his name, described the procedure as performed in a four-year-old child as follows: "An incision was made directly over the tips of 4 spinous processes with kyphos in the center. Each process was split longitudinally for about 1¼ inches into two portions, one-third of the process on the left and two-thirds on the right. The soft tissues between the processes were separated by blunt dissection or by scalpel parallel with the muscles Greenstick fractures were produced at the base of the one-third portions of each of the processes. A wedge-shaped cavity was thus produced, ready to receive the bone graft. A compress of hot saline was placed over the wound A prism-shaped piece of tibia was then removed by means of a chisel with the periosteum intact on 2 of its surfaces The graft taken was about 4 inches by 1 inch by ½ inch It was placed in the interval between the portions of the spinous processes. The dense fascia over the tips of the processes was then approximated by interrupted sutures of No 3 chromic catgut. The skin was closed by continuous suture of number one plain catgut."

In developing the bone graft operation Albee made many suggestions as to details. The length and shape of the required graft are determined by calipers and a flexible probe applied to the gutter bed. If the kyphos is great, the bone graft is cut or molded into a segment of a circle in order that the corners will not project beyond the tip of the spinous processes distal from the kyphos

(Fig. 6). The spinous processes are split with a broad, thin osteotome. After one process has been split, one edge of the osteotome may be anchored in the cleft so as to guide the other edge while it splits the next process above or

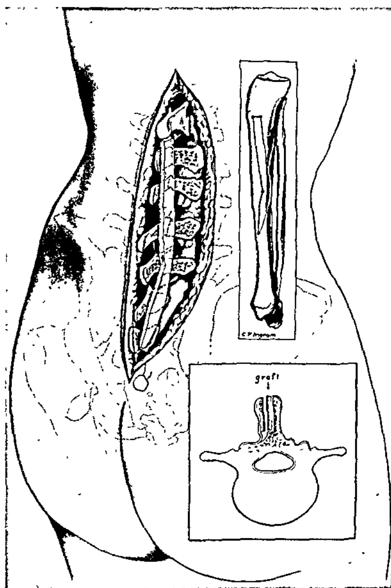


Fig 6—Albee's fusion by massive curved graft of the tibia Upper insert shows method of removing tibial graft Lower insert shows cross section of vertebral body and demonstrates the graft in place. The graft should be in contact with the denuded laminal arch and spinous process Large amounts of cancellous bone should be packed about the graft and the denuded spines.

(Speed, J S. *Operative Orthopaedics*, C V Mosby Company, 1939)

below. Great care must be taken to fracture only one of each pair of spinous process halves The gutter for the graft must be bounded by a row of fractured half-spines on one side and a row of unfractured half-spines on the other, with their split-imbedding ligaments.

The graft from the tibia must be long enough to cover the entire length of the gutter, including that in the intact vertebrae. It must be strong enough to stand the strain to which it will be subjected The shaping of the single graft can be accomplished only to a limited degree. By cutting the upper and lower portions of the graft from the antero-internal surface of the tibia at an angle to the axis of its middle portion, which crosses the tibial crest, one can secure a graft with a greater or lesser curve, but the tibia is not wide enough to provide a single graft suitable for more than a moderate kyphosis. In more extreme cases of kyphosis, Albee recommends the use of the "bundle of reeds" graft.

Grafts

For removal of the graft a skin incision is made along the anteromedial surface of the tibia, and is so placed that its closure will not bring the skin sutures over the bone cavity produced by removal of the graft. The skin is dissected from the periosteum and the muscles freed from their attachments to the outer side of the tibial crest. In general, the graft should include the total thickness of the tibial cortex, i.e., the periosteum, the endosteum, and the marrow, and its width should be three to four times this amount or approximately one-fifth of the diameter of the tibia. The graft must be long enough, in most instances, to include the spines of two healthy vertebrae above and two below the diseased area. With the molded probe serving as a pattern rod, the required graft is outlined on the periosteum of the tibia with a scalpel. The shaping of the graft is most important The graft should bear no corrective stress at the time of its insertion If the kyphosis is extreme, the graft should be cut curved to fit the contour of the kyphosis. The graft is placed in the previously prepared gutter, the supraspinous ligament is closed first over the central portion of the graft and then over its extremities The sutures should be passed deeply enough to get a firm hold upon the ligament and to close the spinous processes to obtain intimate contact between the graft and the raw surfaces of the spinous processes. The muscles and deep fascia are then closed over the graft as is the curved skin incision. The treatment following Albee fusion is recommended for the post-operative treatment of Hibbs arthrodesis

Osteoperiosteal grafts may be used to reinforce the Hibbs fusion or may be used as is the Albee graft when the kyphosis is severe. Lewin and others have pointed out the advantages of such a graft. The osteoperiosteal graft is taken by means of mallet and chisel. An incision of the desired length is made over the tibia as in taking the Albee graft The tibia is exposed with its periosteum left intact. The contour of the graft is outlined with a scalpel through the periosteum An osteotome is then driven into the tibia without disturbing the soft part attachment of the portion to be taken for the graft The osteoperiosteal graft is then raised by means of a chisel with gentle blows by the mallet. If this graft is taken carefully the bone fragments are held together by the fascia and periosteum and the mass can be fitted into the contour of the laminal or spinous process bed.

Whitman described the use of rib grafts to reinforce the Hibbs procedure. He observed in operating on the more advanced types of scoliosis that at the point of maximum curvature, the laminae on the convex side of the vertebrae were so overhung with deformed spinous processes and ribs as to be in many cases

inaccessible. The efficacy of the routine Hibbs operation was thus in these extremely severe cases diminished one-third. It occurred to him that the excised sections of ribs removed to correct deformities in the costal cage might be used as a graft. Their curvature was found to coincide almost exactly with the convexity of the spine. The ribs were sometimes split and sometimes used whole

Petter described the use of multiple rib grafts to reinforce the Hibbs fusion. The grafts are cut into splinters which measure roughly 4 cm. in length and 2 to 3 mm in diameter. For taking the graft an incision is made over the 9th and 10th ribs from the edge of the erector spinae muscle group laterally for a distance of about 15 or 20 cm. The rib to be used is removed subperiosteally by incision and stripping of the periosteum in the same manner as that carried out in the usual thoracoplasty. If sufficient bone cannot be obtained from one rib, segments measuring from 10 to 12 cm. in length are taken from alternate ribs The grafts are placed longitudinally in the laminal beds in contact with the denuded laminae and with each other

OTHER OPERATIVE PROCEDURES

Henry and Geist have described a modification of the Hibbs procedure using multiple chip grafts from the upper end of the tibia which provides both cortical and cancellous bone. A midline incision at least 12 in in length is made extending over the area to be fused Henry and Geist iodize the cut edges of the skin as advocated by Dunn before applying skin towels. The spinous processes and the laminal arches are exposed as described under the Hibbs fusion Next, by using the hand chisel and utilizing the spines for leverage, small thin shavings of bone are removed from the laminae until their exposed surfaces are entirely raw The laminal bone bed is prepared by hand chisels without use of hammering The spinous processes are then removed by bone-cutting forceps. One spinous process at each end of the field to be fused is cut obliquely to avoid disfigurement. A second team in the meantime removes multiple chip grafts from the tibia These grafts are finger nail in size A large handful of grafts is needed Similar grafts are prepared from the removed spinous processes The chip grafts are distributed evenly over the laminal bed and are pressed into contact with the raw laminae and with each other by the use of the blade of a broad raspatory (Fig. 7) The periosteum, muscles, and dorsal fascia are sutured over the grafts in the usual manner. No cast is applied until the end of 12 days, when a plaster of paris body jacket is applied on the Goldthwait irons The patient is kept recumbent for a period of 10 weeks at the end of which time he is fitted with an Osgood type of brace with axillary crutches. This is usually worn for about three months

Gibson described a modified technic of spinal fusion with the use of a bone graft adapted in contour to fit about the spinous processes. His technic overcomes two difficulties: first, adaptation of the graft to a curved contour; second, accurate splitting of the spinous processes themselves. He uses a massive H-shaped graft which is self-retaining. Through a midline incision, the spinous processes are approached subperiosteally. In clearing the processes, attempts are made to roll back with the soft parts on either side a layer of periosteum with a "scraping" of bone on its deep surface The laminae are exposed in a similar

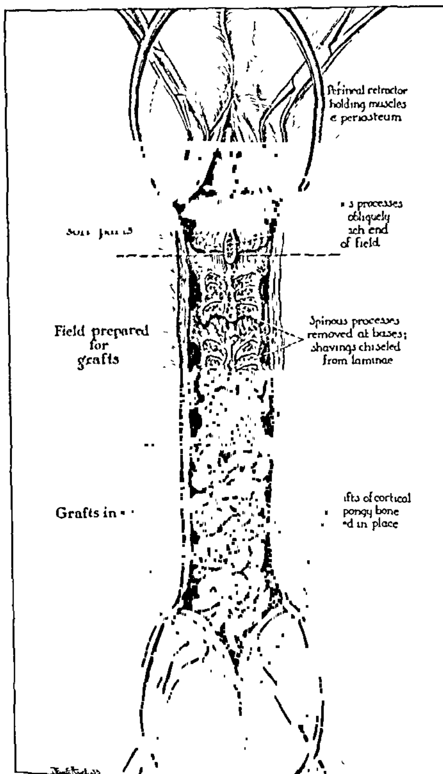


FIG 7.—Henry and Geist multiple chip technic of spine fusion. (Henry, M O, and Geist, E. S *J. Bone & Joint Surg*, *15* 622, 1933.)

manner. The tips of the spinous processes are left intact. This leaves a
like expansion at the tip of the spine covered by a cushion of supraspinc
ments. The spines of the vertebrae to be fused are then amputated lc
flat area of bone on which the graft is to be placed. The sides of two
above and below, are then made raw with the small chips being left in p
The graft is taken from the tibia, its length being equal to the total lc
the spines to be fused. The tibia is exposed as described under Albee fus
the graft is taken by means of an electric saw. With a large blade, fc
are made parallel to one another. The two peripheral cuts extend th
length of the graft The two inner cuts are interrupted so as to leave
corresponding to the graft bed. The central cuts are fairly close together.
blade is then fitted to the saw and cuts are made in each end so as to c
the separation of the graft. When the distal portions of the graft betw
inner cuts are removed, one has a double fishtail or clothespin type g
removing the central distal slivers, the base of the sliver where it is to
free from the graft is narrowed. The groove at one end is made to slid
the raw surfaces of the two upper spines and the sliver is tapped snug
position by blows upon the free end. The engaged fishtail has sufficient sj
glide over the cushioned spinous processes and to be held from spring
again by the elasticity of the bone. To insure that the graft will fit snugly
slivers are tapped in between the limbs of the fishtail graft and the
processes at the upper and lower poles of the fused area. Bone chips a
packed about the graft and along its under surfaces Since Gibson's paper
other similar modifications have been reported. Most operators now
attempts to fuse the articular facets with this procedure

Bosworth has described the use of the clothespin or H-shaped graft,
he advocates on the basis that if graft placement can be solidly maintai
the shape of the graft alone without other fixation, results of attempts a
rodesis are improved. The H graft is cut with the ends notched to rece
spinous processes at either end of the fusion area. Grafts may be taken fr
tibia or from the ilium. After the routine Hibbs type laminal bone bed ha
prepared, the operating table is adjusted and the patient is placed with tl
to be fused in flexion to separate the spinous processes. The graft is then
with the notched ends fitted about the spinous processes at the end of tl
to be fused. The patient is then extended with the graft locked into posi
the spinous processes. The H graft is reinforced by separate iliac strips
underneath in contact with the posterior elements of the vertebrae (F
Bosworth has observed that separation of the posterior elements of the
column was not only found to occur owing to the leverage action of the gr
because separation of the anterior elements occurs as well He is of the c
that the intervertebral foramina of the grafted area are enlarged by the c
tion. In the early cases Bosworth used plaster jackets applied immediatel
operation. The jacket is now generally applied two to three weeks postope
Where the massive graft has been fashioned of iliac bone, the patient is
ambulatory immediately following cast applications. For accurate estimat
spinal fusion, roentgenograms in flexion and extension, and right and left
flexion are recommended by Bosworth.

Allison described a fusion operation of the spine in which he combines bilateral osteoperiosteal grafts with the Hibbs procedure. The surgical approach is the same as described for the Hibbs technic. An incision is made in the midline over the tip of each spinous process dividing the supraspinous ligaments in a true

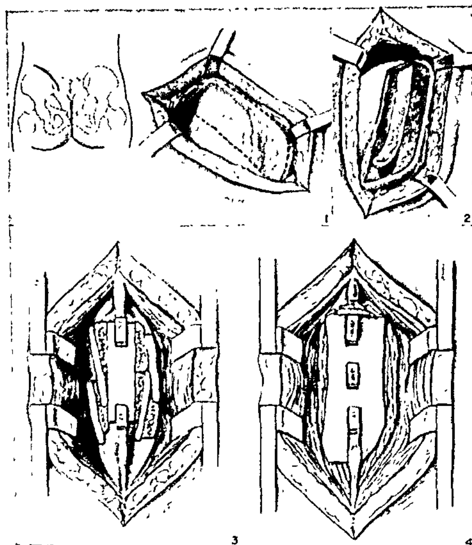


FIG 8—Clothespin graft as advocated by Bosworth (1) Site of iliac incision and outline of massive iliac graft used for clothespin (2) Cancellous iliac strips to be packed about the massive graft. (3) Clothespin graft in place with cancellous strips packed about its periphery. (4) When two or more vertebrae are to be included in the fusion with the sacrum, the H portion of the graft may be cut to fit about the spine of the sacrum and the spine of the uppermost vertebra. The crossarm of the H may be windowed to receive the spinous processes of intervening vertebrae

(Bosworth, D M *Am J Surg*, 67 61, 1945.)

mid-vertical line. He suggests that this be done by securing each spinous process in the grasp of a curved clamp and making a vertical knife cut in the mid-sagittal plane of the spinous process. From this entrance point the muscles, fascia, and periosteum may be stripped from the side of the process along the laminae below. In preparing the bony bed he turns down a bone shaving from each

lamina as far as the lateral articulation, with the chisel being driven into the lateral articulation. Following this, the articular cartilage is removed by a chisel and small curets. The spinous process is then split longitudinally into three fragments with a chisel and the spiny process is cut across at its base so that these fragments may be broken down to lie in position overlapping the space between the spinous process above and that below. In this manner the entire

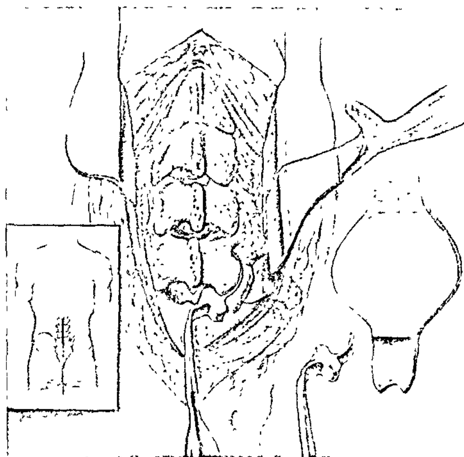


FIG 9.—King recommends the use of a notched Bennett retractor for exposure of the lateral articulations and special osteotome for removal of articular facet from articular cartilage (King, D *Am J Surg*, 66 357, 1944)

area of the posterior spinal arch is bridged with bony fragments, each of which is still loosely attached to a base The fragments are flattened out so that the surface is a rough surface of fractured bone and continues from the upper limit to the lower limit of the area to be fused. On each side of the midline an osteoperiosteal graft from the tibia is placed with the bone side down, the two strips of the osteoperiosteal material being one-half inch wide and long enough to reach the limits of the denuded area. He secures his osteoperiosteal graft in a manner similar to that described by Lewin The closure is in the usual manner. For postoperative care he recommends the use of a firm mattress and states that that is all that is necessary for the first 10 postoperative days. After removal of

the sutures and when the wound healing is established, the patient is supplied with a suitable brace or a plaster of paris shell. Absolute recumbency is used for a period of eight to 12 weeks. Supportive protection of the spine as well as carefully planned supervision of activity is recommended for at least one year after the operation.

King, seeking a method for fusion of the spine in which immediate rigid internal fixation could be secured, described the use of vitallium screws across the articular facets. To test the strength of the facets and the rigidity of the fixation

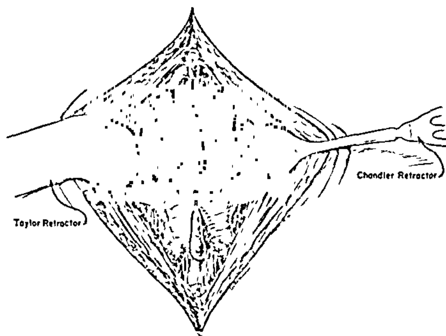


FIG. 10—Methods of exposing the articular facets by the Taylor retractor or the Chandler retractor
(Baker, L. D., and Hoyt, W. A., Jr. *South. M. J.*, *41*: 419, 1948.)

the operation furnishes, the procedure was done on fresh cadavers. With the cadaver in the prone position, a hook was placed under the fifth neural arch and upward traction made with a rope passing over a ceiling pulley. It was found that small and medium-sized cadavers could be raised from the table without the fixation giving way. In one very heavy cadaver, just as the trunk cleared the top of the table with the legs and arms still touching, the laminae fractured on either side of the hook under the spinous process without disruption of the screw fixation. In another instance in a heavy cadaver, the arch gave way bilaterally at the screw holes.

The patient is placed on a hinged table, the lumbar lordosis being partly obliterated by lowering the head and foot of the table. The surgical approach as described under the Hibbs procedure is performed. The intraspinous and supraspinous ligaments and all soft tissues are carefully removed from the area to be fused. The lateral articulations are exposed by dissection and scraping away the posterior portion of the joint capsule. For this exposure, King uses a notched Bennett long bone retractor (Fig. 9). A Chandler elevator or a

Taylor retractor may be used (Fig. 10). Either instrument allows excellent leverage and full exposure of the surgical field. As much as possible of the

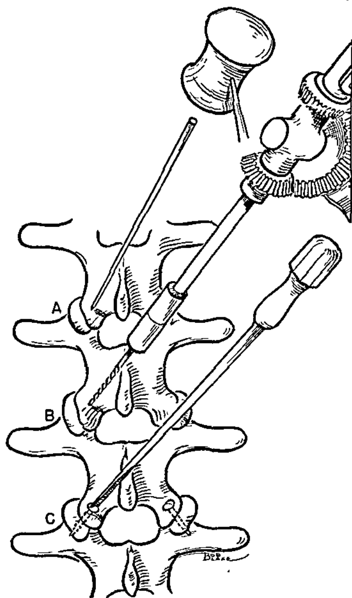


Fig 11 —(A) Impression is made in the presented facet by means of a long pointed steel instrument (B) A hole drilled through the contiguous facets A long drill point will aid in preventing *the spinous process or the laminal arch from blocking the shank of the drill (C) Insertion of* the screw

(Baker, L D, and Hoyt, W A, Jr *South M J*, *41* 419, 1948)

articular cartilage of the facets is removed, and a flat thin flexible cautery tip is then inserted into the joint and the remaining cartilage cauterized. The fifth lumbar spinous process is removed and put aside to be used as a graft A notch is then placed in the middle of the cortical surface of the superior articular facet of the fifth lumbar vertebra for the reception of the tip of a No 31 drill

This notch prevents slipping of the drill point when it begins to rotate. The drill is directed downward and outward parallel to the inferior edge of the fifth lamina. The resulting tunnel will pass through the midline of the two facets and on into the lateral mass of the sacrum. A vitallium screw is placed in the tunnel and tightened, and the same procedure is carried out on the opposite site (Fig. 11). Rigid lumbosacral fixation can be demonstrated by seizing the stump of the fifth lumbar spinous process with a heavy Kocher hemostat and

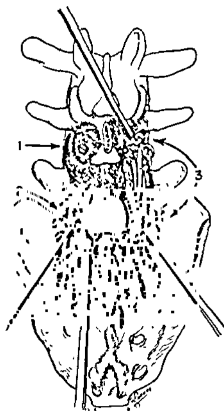


FIG 12 —(1) After the articular cartilage has been excised from the facets and the screw has been placed across the joint the laminal arch and the periphery of the facets and the pedicle are denuded of cortical bone (2) Small chips are then laid about the denuded articular surfaces (3) Grafts cut from the excised spinous processes The laminae and sacrum are then placed in the fresh bony beds. Additional grafts from the iliac crest are used as needed

(Baker, L D, and Hoyt, W A, Jr *South M J*, *41* 419, 1948)

lifting toward the ceiling. If additional vertebrae are to be fused, similar processes are carried out between the respective articular facets. The remainder of the operation consists of elevating multiple small bone chips from the laminal arches and from the dorsal surface of the sacrum (Fig 12) Supplemental bone grafts from the ilium or tibia are always used by King, iliac bone being preferred (Fig 13)

Anderson has described the use of finely chopped grafts placed along lateral troughs. His exposure is essentially the same as that as described by King. The second step is to remove the dorsal portion of the lamina and all of the inferior articular facet in one piece The superior facet of the vertebra below

is then denuded of cartilage and the dense subarticular bone down to cancellous bone is resected. The posterior surface of the pedicle is chiseled down to bleeding bone In the meantime an assistant has cut the fragments from the spinous processes and the laminae into tiny grafts the size of "grapenuts." These crumbs are poured into the lateral troughs formed by the excision of the dorsum of

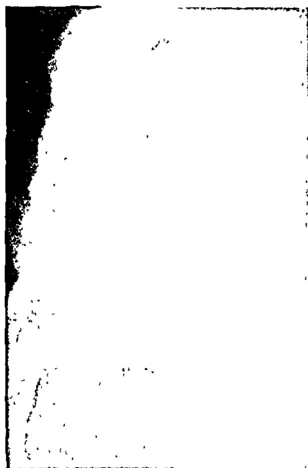


Fig 13 —Lateral view of lumbosacral spine showing bony fusion Five years follow-up (King's arthrodesis).
(King, D *Am J Surg*, 66 357, 1944)

the laminae and facets. If the crumbs, after they are packed down firmly, do not come to the level of the vertex of the remains of laminae, additional bone should be obtained from the crest of the ilium or from fresh donor or bank bone. The muscles are lifted up over the crumb grafts, care being taken not to displace the fragments, after which the tissues are closed in the routine manner (Figs. 14 and 15).

A thick cotton compression dressing is placed over the wound Anderson emphasizes the importance of the spinal muscles holding the grafts which have been placed laterally so that the large spinal muscles will lie directly over the laterally placed mounds of small chip grafts.

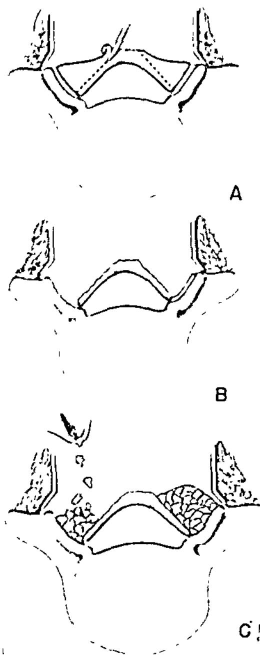


FIG 14.—(A) Removal of the dorsal portion of the lamina and all of the inferior articular facets (B) Articular cartilage removed from the superior facet of the vertebra below (C) Tiny grafts being placed about the lateral trough formed by excision of the lamina and the articular facets.

(Courtesy of Dr Roger Anderson)

Chandler has described the use of vertical and transverse iliac grafts combined and held by 18-8 wire. His incision and approach to the spine, laminae, and articular facets are as described under the Hibbs and King procedures He emphasizes radical treatment of the lateral articulations which he resects with a thin osteotome. Following this, he makes three longitudinal incisions in the adjacent bone of the facets, then, with the use of an impactor, he breaks the

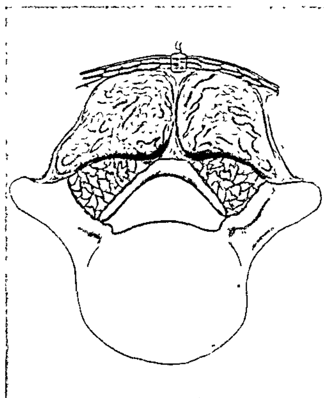


FIG 15 —Cross section of the wound showing the grafts in the prepared bony bed with the muscles lifted up and over the crumb-size grafts
(Courtesy of Dr. Roger Anderson)

adjacent bone down and impacts it into the debrided joints using additional cancellous bone if necessary to pack about the joint. After the laminae are denuded thoroughly of their cortical bone and all articular facets have been treated as described above, iliac grafts are inserted in the following manner· The first two grafts are placed with their cancellous surfaces down in contact with the denuded laminae to be fused. Two additional grafts are then placed in horizontal positions in the interspinous spaces between L_4 and L_5, and L_5 and S_1. The latter two grafts are notched to fit well about the inferior surface of the spine above and the superior surface of the spine below, and they are made sufficiently long to overlap the two grafts placed in contact with the laminae. An 181-8 wire previously placed between drill holes in the upper portion of the spinous process of L_4 and in the lower portion of the first sacral spinous process is then tightened to stabilize the fused spine and to hold the grafts snugly in place

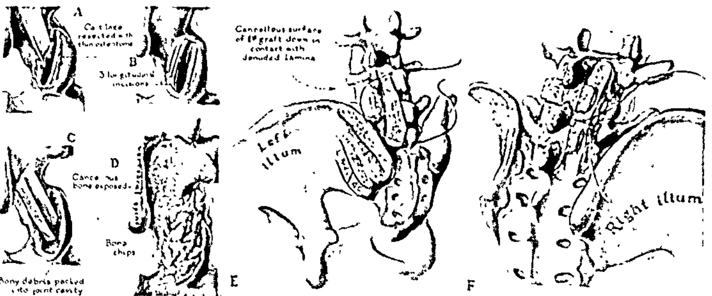


FIG. 16 – Chandler's technic for lumbosacral fusion (A) Articular facet cartilage removed with a thin sharp osteotome. (B) Denuded facets incised longitudinally (C) Impactor used to break down the fragments from the facets (D) Laminal arches denuded of cortical bone, bone chips packed about the facets. (E) Iliac grafts The first graft is placed with the cancellous surface in contact with the denuded laminae The second graft is placed in a similar position on the opposite side The third and fourth grafts are used as demonstrated in (F). (F) The transverse grafts are notched to fit about the spinous processes; 18-8 wire, previously inserted through drill holes in the upper portion of the spinous processes of lumbar 4 and through the lower portion of the first sacral spinous process, are tightened to immobilize the fused spines and to hold the grafts in apposition

(Courtesy of Dr Fremont A. Chandler.)

(Figs. 16 and 17). Chandler is of the opinion that no external support is needed and the patient is permitted to be up and about as soon as he desires

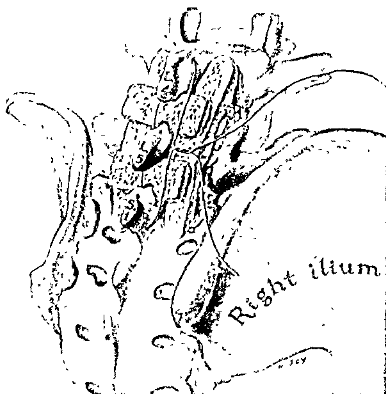


FIG 17 —Chandler's method of using vertical and horizontal grafts to reinforce the Hibbs type of fusion The vertical grafts are placed laterally over the denuded laminae and the excised articular facets The horizontal grafts are notched and fitted into the interspinous spaces The grafts are held in place by an 18-8 wire previously placed between drill holes in the upper portion of the spinous process of lumbar 4 and in the lower portion of the first sacral spinous process The wire is tightened to stabilize the spine and to hold the grafts snugly in place. (Courtesy of Dr Fremont A Chandler)

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